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NOTE ON THE SPINAL CORD OF THE FINBACK WHALE (*BALAENOPTERA PHYSALUS*)

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Submitted for publication, June 15, 1935

The Cetacea, of all the orders of mammals, are the most highly specialized for an aquatic mode of life, as strikingly indicated, for example, by the extensive alterations in the form of the skull, by the reduction of the forelimbs to flippers, by the exceedingly vestigial character of the hindlimbs, and by the modification of the tail into the prime organ of locomotion. Undoubtedly they are the descendants of an original terrestrial stock that secondarily has become adapted to life in the water (Kellogg, 1928). They thus represent an interesting experiment of Nature, and consequently their structural and functional peculiarities have long engaged the close attention of anatomists and physiologists (see Howell, 1930).

The nervous system, and more particularly the brain, has been studied in a number of specimens, especially with a view toward ascertaining whether it has been subjected to any peculiar modifications with adaptation to aquatic life. The spinal cord, however, and more specifically its microscopic structure, has received less attention. Of the published studies on the cetacean cord, those of Cunningham (1877), Guldberg (1885), Ziehen and Kükenthal (1893), Hatschek (1896a), Rawitz (1903), Hepburn and Waterston (1904), and Langworthy (1932) are to be noted. Yet, of these investigations, all but two (Guldberg, Rawitz) deal only with the Odontoceti or toothed whales. Guldberg's study of the spinal cord in two specimens of the Mysticeti or whalebone whales, both *Sibbaldus musculus* (= *Balaenoptera Sibbaldii* and *B. musculus*), was limited to the cervical region, as was that of Rawitz on an example of *Balaenoptera acutorostrata* (= *B. rostrata*). Thus, as far as I have been able to ascertain, nothing is known about the remainder of the cord in the whalebone whales.

Through the kindness of Dr. E. M. K. Geiling, I have been able to

study a portion of the spinal cord of a 56½-foot female finback whale, *Balaenoptera physalus*, obtained by him during the summer of 1934, off the Queen Charlotte Islands. The specimen represents a portion of the upper thoracic cord, more exact allocation being impossible. Although this is but a fragment, in view of our paucity of knowledge regarding the spinal cord of the Mysticeti, its careful study seems justifiable. The portion of cord was preserved, with membranes intact, by submersion in 10 per cent formalin. For this reason its fixation is not all that might be desired, yet the more important details can readily be observed. Sections stained with hematoxylin-eosin (15 micra thick), gallocyanin (15 micra), Mallory's (15 micra), and Pal-Weigert (40 micra), have been studied. All my measurements of relative areas of this and other mammalian cords were taken with a planimeter from enlarged drawings of transverse sections obtained by use of the Edinger projection apparatus.

The spinal dura mater is tough and of excessive thickness. The pia-arachnoid is extremely vascular, the vessels forming a sort of rete mirabile, a circumstance also noted by Cunningham and Hatschek in porpoises. The cord itself is nearly cylindrical, the dorso-ventral and transverse diameters of a typical section (the dura being removed) measuring 17 and 16 mm., respectively; this rotundity also has been observed in the pike whale, *Balaenoptera acutorostrata* (Rawitz), and in the porpoises, *Delphinus delphis* (Hatschek) and *Phocaena phocoena* (= *P. communis*) (Hepburn and Waterston). The dorsal roots appear to be relatively small in comparison to the ventral roots, as in porpoises (Cunningham, Hatschek, Rawitz); this arrangement is in marked contrast to the usual condition in mammals. The ventral longitudinal fissure is very deep, extending for fully half the depth of the cord, and thus nearly reaching the base of the gray substance, so that the ventral white commissure is comparatively small. On the other hand, both the dorsal longitudinal sulcus and septum are entirely absent in some sections, while merely vestiges of the latter are apparent in others; these conditions also occur in both *Phocaena* (Rawitz, Hepburn and Waterson) and *Delphinus* (Hatschek). It should be mentioned that whereas Guldberg found a dorsal fissure present in the spinal cord of a fetal *Sibbaldus*, it was completely absent from the cervical cord of an adult that he examined. The central canal of my specimen is entirely

obliterated, and even its ependyma cannot be recognized with certainty, although possible vestiges are suggested in some sections. This complete obliteration of the central canal is a regular occurrence in the cetacean cord, having been noted by Guldberg (in *Phocaena*, entire cord), Hatschek (in *Delphinus*, entire cord), Rawitz (in *Phocaena* entire cord; *Balaenoptera*, cervical cord, only portion studied), and

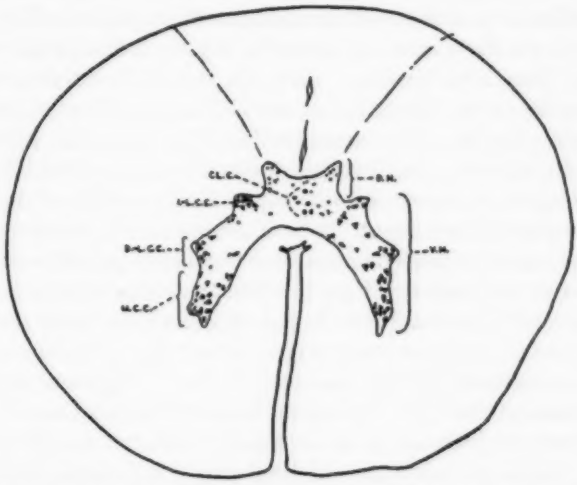

FIG. 1. TRANSVERSE SECTION OF UPPER THORACIC CORD OF ADULT FEMALE FINBACK WHALE (*Balaenoptera physalus*)

Drawn from a hematoxylin-eosin section. Some of the details have been filled in from other sections. The relative size of the cells has been exaggerated. CL. C., Clarke's column of cells (nucleus dorsalis); D. H., dorsal horn; D.-L. C. C., dorsolateral column of ventral horn cells; I.-L. C. C., intermediolateral column of cells; M. C. C., medial column of ventral horn cells; V. H., ventral horn.

Hepburn and Waterston (in *Phocaena*, entire cord). Hatschek clearly recognized the ependyma of the canal, while Hepburn and Waterston saw indications of its remains in the middle of the gray commissure. It should be noted, however, that in contrast to the above, Langworthy appears to have found a patent central canal in at least the upper cervical cord of the porpoise *Tursiops truncatus*.

The gray matter appears to be relatively small, even for the thoracic

region, this being chiefly the effect of the reduced size of the dorsal horns. The stunted appearance of the latter, together with the great divergence of the ventral horns, produces a marked departure from the typical H-shaped configuration of the gray matter so characteristic of the thoracic cord of other mammals. The spinal gray matter appears uniformly to be of relatively meagre development in all Cetacea, when comparison is made with other Mammalia. From the descriptions and figures of the several authors, it seems likely that the gray is relatively more diminished in Mysticeti than in Odontoceti (also see Hatschek, Rawitz). Although the slight development of the dorsal horns (Guldberg, Ziehen and Kükenthal, Hatschek, Rawitz, Langworthy) is the chief factor in this diminution, the restriction of the ventral horns in the lower cervical and lumbar regions (Hepburn and Waterston), in correlation with the vestigial character of the limbs, also is a contributory agent. I have compared the relative area of the gray matter in my specimen of *Balaenoptera physalus* with the same proportion computed from the thoracic cords of other mammals. An unavoidable technical error is probably present in these computations, on account of the variability in shrinkage accompanying fixation in the different animals, and on account of the personal equation in determining the exact boundaries between gray and white. This error, however, probably is of no great significance for the present study. In the finback whale the total gray area is 8 per cent of the total white area, in the rock wallaby (*Petrogale*) 6 per cent, in the kangaroo (*Macropus*) 8 per cent, in man (*Homo*) 9 per cent, in the gray fox (*Urocyon*) 10 per cent, in the agouti (*Cuniculus*) 13 per cent, in the Australian opossum (*Trichosurus*) 14 per cent, in the rhesus monkey (*Macaca mulatta*) 15 per cent, in the spider monkey (*Ateles*) 17 per cent, in the white rat (*Rattus*) 29 per cent, and in the kangaroo rat (*Dipodomys agilis*) 62 per cent. The relatively small size of the gray matter as found in the whale thus is by no means unique. In contrast to wallaby, kangaroo, fox and man, however, it is the sensory (dorsal) gray that is especially dwarfed. On the other hand, the large figure for the kangaroo rat may be explained by the great development of the dorsal horns in this animal. An uncontrollable variable in these computations is introduced by the white matter, which might, conversely, be regarded as relatively large in such forms as man, fox,

kangaroo and wallaby. Indeed, Kappers (1920) showed that the growth of the spinal gray matter tends to lag behind that of the white matter phylogenetically, and that in animals belonging to the same order the larger might be expected to possess relatively less gray (or more white). At any rate, the Cetacea appear to be unique among Mammalia in regard to the poor development of the dorsal gray. The significance of this character will be discussed later.

Each ventral horn is long and slender. The ventral half of its lateral border slants sharply inward; hence the gray matter tapers markedly in a ventral direction, with resultant formation of a prominent projection at the middle of its ventrolateral border. Many large, multipolar cells, containing numerous Nissl bodies, and of typical motor form, are scattered throughout the ventral horn proper. They may be divided, more or less definitely, into two groups. One group, containing by far the greater number of cells, occupies the ventral and more medial portions of the horn, and doubtless represents the so-called medial cell group, which is known to innervate the intrinsic back or myotomic musculature in other mammals. The other and much smaller group is located more dorsolaterally, occupying the aforementioned prominent projection along the lateral border of the horn and the adjacent gray. The components of this group presumably innervate the ventral thoracic and abdominal muscles derived from the more ventral portions of the myomeres. The difference in number of cells occupying these areas of the ventral horn is of particular interest, and in no wise surprising; for, in comparison even to the strong ventral thoracic and abdominal muscles, the intrinsic back muscles of cetaceans are enormously developed and of excessive thickness (cf. Howell).

The dorsal horns, being so short and dwarfed in form, consequently terminate far from the surface of the cord. The cells of this region are small, and but few in number. A substantia gelatinosa Rolandi is entirely lacking. This latter sensory component appears regularly to be absent in both groups of cetaceans (Guldberg, Hatschek, Rawitz). Hepburn and Waterston, however, believed that this structure was present in the cord of the *Phocaena phocoena* that they studied. Wilson (1933) likewise indicated that a substantia gelatinosa occurred in the upper cervical cord of the sulphur-bottom whale,

Sibbaldus musculus (= *Balaenoptera sulfurea*), but he stated that it was very poorly developed. In my specimen, no reticular formation can be identified. Clarke's column (nucleus dorsalis) is peculiar in that—in comparison to conditions in other mammals—it is displaced ventrally and medially, lying near the middle of the well developed gray commissure in the region around the obliterated central canal. Furthermore, one cannot accurately speak of this nucleus as a bilateral structure, for actually there appears to be but one such cell-group, situated near and around the midline. The relationships of the cells suggest that this median structure has been formed by fusion or consolidation of the Clarke's columns of the two sides. This tendency for the cells of Clarke's columns to occupy a locus near the middle of the gray commissure, and to form a single median nucleus, has also been noted in *Phocaena* (Rawitz, Hepburn and Waterston) and *Delphinus* (Hatschek). The component cells of Clarke's nucleus are typically large, roundish or ovoid, and contain Nissl bodies that perhaps are more diffusely arranged than in the neurons of either the ventral horn or the intermediolateral cell-column. These cells are by no means numerous, only seven or less being present in a single section, this being in complete agreement with the observations of Rawitz on the thoracic cord of *Phocaena*. In the Pal-Weigert sections of *Balaenoptera physalus*, it can be seen that the cells of Clarke's column are more or less encircled by a conspicuous, heavy ring of longitudinally coursing medullated fibers. Hatschek appears to have found a similar circumferential band of white fibers in *Delphinus*, while Rawitz saw two longitudinal bundles of white fibers in close relationship to Clarke's cells in *Phocaena*. Doubtless these are similar to the fibers seen by me. A number of other cells, mostly small, are scattered throughout the commissure and the adjacent gray.

Just opposite the middle of the gray commissure in the finback whale is a prominent lateral projection of the gray substance—the lateral column—containing the intermediolateral group of sympathetic cells. These, numbering from 5 to as many as 17 on a single side in individual sections, contain well marked Nissl bodies, and in general are not markedly smaller than the cells of the ventral horn proper. There is no group of cells that might definitely be identified as the so-called sympathetic sensory nucleus of Bechterew.

The lateral columns of white fibers are very much larger than either the ventral or dorsal columns, the latter being especially small. As in my specimen, Hepburn and Waterston found in *Phocaena* that the lateral columns of white fibers regularly occupied a much greater area than the ventral columns; while the same relationship is evident from the illustrations of Rawitz for both *Phocaena* and *Balaenoptera acutorostrata*. Langworthy, however, emphasized the enormous development of the ventral columns, which were much larger than the lateral, in *Tursiops truncatus*.

As stated above, the dorsal white columns appear to be relatively small. This perhaps is not surprising in view of the reduced character of the sensory gray. One of the most striking features of the cetacean spinal cord relates to this relatively small size, at all levels, of the dorsal columns of white fibers, when comparison is made with the remainder of the white substance. This is a character that has drawn comment from virtually all investigators. It is common to both the Mysticeti —*Balaenoptera acutorostrata* (Rawitz) and *Sibbaldus musculus* (Guldberg, Wilson)—and the Odontoceti—*Delphinus delphis* (Hatschek), *Hyperoodon ampullatus* (= *H. rostratus*) (Ziehen and Kükenthal), *Phocaena phocoena* (Rawitz, Hepburn and Waterston), and *Tursiops truncatus* (Langworthy). Brouwer (1915), however, in his extensive and highly valuable comparative anatomical study of the development of the dorsal white columns, found these structures to be relatively large in *Phocaena*. With respect to relative size of the dorsal funiculi (their area being expressed in percentage of the total area of the white matter at the level of the uppermost cervical segment), Brouwer found *Phocaena* to be surpassed by only three animals, namely, man, elephant and capuchin monkey, among a series of 20 forms representing individual genera of a variety of mammalian orders. There seems to be some question here. The measurements of Hepburn and Waterston for *Phocaena phocoena* at the level of C 1, when computed so as to be comparable with those of Brouwer, give a somewhat smaller percentage value for the area of the dorsal columns (20.06, in contrast to Brouwer's 25.90), a value which would relegate this animal to the lower levels of Brouwer's list. The matter of individual technique in arriving at such estimates, as well as individual variability within a species, are of course to be taken into account. Yet it perhaps is

significant that Dexler and Eger (1911), using a method different from those of either Brouwer or Hepburn and Waterston, found that the dorsal funiculi in the upper cervical region were relatively smaller—when compared to the lateral and ventral funiculi—in Cetacea (*Delphinus*, *Hyperoodon*, *Sibbaldus*) than in 12 of the other 13 representative mammals that they studied. The thirteenth animal, the marsupial *Phascolarctus*, possessed dorsal columns of the same comparative size as those of *Delphinus*, but relatively larger than those of *Hyperoodon* and *Sibbaldus*. In order to gain further information on this point, I have measured the area of the dorsal columns of the thoracic cord of my specimen of *Balaenoptera physalus*, and have expressed this in percentage of the total area of the white matter at this level. The resultant value is 15 per cent. Values procured by measurement of comparable sections from other mammals are as follows: Kangaroo, 10 per cent; Gray fox, 11 per cent; Australian opossum, Rock wallaby and Kangaroo rat, all three 15 per cent; White rat, 18 per cent; Agouti, 20 per cent; Rhesus monkey, 22 per cent; Spider monkey, 26 per cent; and Man, 28 per cent. In the thoracic region, therefore, in respect to relative size of the dorsal white, the whale is located near the bottom of the list of available animals, but the contrast with other mammals, if we except the primates, is not striking. Yet on the whole the result obtained is in closer agreement with those of Dexler and Eger than with those of Brouwer. The thoracic region, however, is not a particularly good one for such a comparison, for the dorsal column fibers from the upper extremities thereby are excluded. The upper cervical region undoubtedly gives the representative picture for the entire animal, but in the present instance, unfortunately, this part of the cord is unavailable for study. I deem it quite likely, however, in view of the striking reduction of the cetacean forelimbs, that upper cervical sections from *Balaenoptera physalus* would forcefully emphasize the relatively small size of its dorsal white columns, in comparison to most of the other mammals studied. It might seem surprising, when one considers the extremely vestigial character of its hindlimbs, that the whale does not exhibit even smaller dorsal funiculi in the thoracic region. Explanation for this may reside in the fact that the tail has become such a highly specialized organ for locomotion, with probably well developed proprioceptive component, which fibers

would be present at thoracic levels. Similarly, the comparatively large thoracic dorsal columns of the spider monkey might be accounted for by its highly prehensile tail, which acts almost as an extra hand.

In the cord of the finback whale, one receives the impression that the fibers near the periphery of the white matter are the more heavily medullated, though perhaps this decision is influenced by the incomplete fixation of the specimen; for the myelin of the deeper fibers clearly has suffered degeneration. In the periphery of the dorsal funiculus, many very large fibers can be seen, yet scattered among them are a number of quite small, poorly myelinated axons. Numerous large, thinly medullated fibers are present in all three funiculi. At this level, at least, there is no septum dividing the dorsal funiculus into medial (fasciculus gracilis) and lateral (fasciculus cuneatus) groups of fibers—similarly absent from the cervical region of *Sibbaldus musculus* (Guldberg) and throughout the whole cord of *Phocaena phocoena* (Hepburn and Waterston)—nor is there any difference in myelinization of these two areas, such as Langworthy found in the thoracic region of *Tursiops truncatus*, in which the medial fibers were more heavily myelinated than the lateral.

A great many septa, formed by inward prolongations of the connective tissue surrounding the circumferential blood vessels, penetrate the white substance for various distances. These septa contain blood vessels, many of which are of good size. The vessels of the gray frequently are large and numerous, especially in the region of the gray commissure. Hence the vascularity of the cord is most striking. In other cetaceans, also, the internal blood supply of the spinal cord is profuse. Many vessels have been noted in the gray matter, especially the commissure, of *Balaenoptera acutorostrata* (Rawitz), *Delphinus* (Hatschek) and *Phocaena* (Guldberg, Rawitz); and also in the white matter of *Balaenoptera* (Rawitz) and *Phocaena* (Hepburn and Waterston), frequently entering this region with the penetrating septa of connective tissue.

The chief features of the cetacean spinal cord refer to the reduction or slight development of the motor limb nuclei and the vestigial or rudimentary state of the sensory components. The former would be expected in view of the reduced character of the forelimbs and the

completely vestigial nature of the hindlimbs. Thus, in *Phocaena*, the nuclei of the hindlimb are much more curtailed than are those of the forelimb (Hepburn and Waterston). The motor nucleus of the powerful tail muscles, on the other hand, is well developed (Hepburn and Waterston). In the remainder of the cord the motor component is of considerable magnitude. The largest group of ventral horn cells are those concerned with the innervation of the greatly hypertrophied back musculature, which assists that of the tail proper in locomotion. The long descending pathways from brain to spinal cord seem not to be well developed. Thus the cortico-spinal tract is relatively small in *Sibbaldus* (Wilson), *Phocaena* (Gierlich), *Tursiops* (Langworthy), and *Delphinus* (Hatschek and Schlesinger, Gierlich) (also *cf.* Gans). Langworthy, studying Weigert preparations, could not follow the fibers into the cord. The corticobulbar tract, however, is very much larger (Gierlich, Wilson). This rather feeble development of the corticospinal system undoubtedly is to be correlated with the reduction of the limbs. Furthermore, Langworthy noted in *Tursiops* that the other long descending systems—the rubrospinal, vestibulospinal and tectospinal tracts—were by no means large, while the medial longitudinal fasciculus was inconspicuous in the region caudal to the vestibular nuclei.

The sensory components of the cord, as already indicated, are feebly constituted. The dorsal roots, the dorsal horn of the gray matter and the dorsal columns of white fibers are all relatively small, while a substantia gelatinosa is entirely absent. These conditions strongly suggest that both cutaneous and proprioceptive sensibility are but poorly developed in the Cetacea. Further evidence for this conclusion is to be found in the relatively small size of the corresponding ascending pathways in the cetacean brain. Thus the spinothalamic tracts are small in *Tursiops* (Langworthy). This harmonizes with the well known fact that the skin of whales is extremely thick, hairless, and relatively insensitive. The proprioceptive pathways to both thalamus and cerebellum likewise are comparatively small (Langworthy), and the nucleus gracilis (especially) and nucleus cuneatus relatively undeveloped (Kappers, Wilson). As might well be expected, however, a conspicuous tail nucleus (or *Schwanzkern*) of Bischoff regularly is present in the medulla (Hatschek and Schlesinger, Kappers, Rawitz 1909, Wilson). Lack of development of the proprioceptive pathways could

be explained by the limited postural changes possible to whales, the result, at least in part, of the vestigial character of their extremities. As already suggested, it is likely that a considerable portion of the proprioceptive fibers that run in the dorsal columns arise from the region of the tail (also *cf.* Hatschek). Other adjustments to proprioceptive stimuli probably are accomplished through short intersegmental fibers limited to the spinal cord itself.

The relative reduction of the spinal sensory components appears to be less extreme in toothed whales than in whalebone whales (*cf.* Hatschek, Rawitz), despite the more advanced reduction of the extremities in the former group (*cf.* Howell). A possible explanation of this may reside in the fact that the smaller Odontoceti are essentially littoral forms, more active than the larger pelagic Mysticeti.

Since the long ascending and descending pathways are so poorly developed in cetaceans, the question naturally arises as to the nature of the majority of the fibers in the large ventrolateral white columns. It seems very likely that many, if not most, of these are short intersegmental fibers (ground bundles or fasciculi proprii) so necessary for the proper correlation of the large axial muscles in swimming, as already suggested by Hepburn and Waterston and by Langworthy. In this circumstance, however, it is difficult to understand the absence of a substantia gelatinosa, the cells of which in other mammals give rise to the fibers of the fasciculi proprii (*cf.* Winkler). No doubt other neurons of the dorsal horn perform this function. In a single section, however, there is considerable discrepancy between the number of apparent intersegmental fibers (many) and that of dorsal horn cells (few). But it should be realized that the individual spinal segments of the whale are very long, and hence must contain many cells; furthermore, it is not impossible that the fibers of the proprius systems may cover more segments than in other mammals.

The vascularity of the cetacean cord, both circumferentially and internally, is very marked. This parallels the well known occurrence of retia mirabilia in other parts of the cetacean body. It has been suggested that these plexuses serve the function of blood reservoirs during the long periods of submergence in the water. The necessity for some such arrangement for the brain and cord in particular is easily comprehended.

Finally, it should be noted that lack of development or reduction of

spinal sensory components, as found in the Cetacea, is not a necessary outcome of an aquatic mode of life. In other orders of aquatic mammals, namely, the Sirenia, studied by Dexler and Eger (1911), and the Pinnipedia, studied by Hatschek (1896b), these conditions—such as smallness of dorsal funiculi and dorsal gray—by no means are indicated. Hence these specializations of the Cetacea appear to be more or less peculiar to this order.

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FINGERAGNOSIA (GERSTMANN)

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In 1924 Gerstmann (1) in Vienna, in examining into the *Körperschema* in the case of a 52-year-old woman, who some time previously had suffered a cerebral accident, discovered a total inability to recognize, indicate on command, name, or choose the individual fingers of both of her own hands and the hands of others. The patient had previously been unaware of this difficulty. There was also present a certain lack of freedom in the movements of individual fingers, although sensory and motor ability were completely intact. This Gerstmann regarded as secondary to the gnostic difficulty. Gerstmann called this isolated defect in the *Körperschema* "fingeragnosia," from the importance of this difficulty, although further examination also disclosed as associated features right-left disorientation, especially for parts of her own body and of the bodies of others, "pure" agraphia, (marked difficulty in spontaneous writing, with copy relatively intact), and acalculia. By 1927 Gerstmann (2) had accumulated two more cases, always with the same syndrome of fingeragnosia, right-left disorientation, agraphia and acalculia. He regarded fingeragnosia, right-left disorientation and pure agraphia as the essential elements of the new syndrome, with perhaps acalculia standing in a close but less essential connection. In all three cases all aphasic, apractic, or other agnostic features were absent.

Since Gerstmann's original contribution, other cases of fingeragnosia with individual variants in the other features of the syndrome have been reported by Hermann and Pötzl (3) (1926), Schlesinger (4) (1928) Isakower and Schilder (5) (1928), J. Lange (6 and 7) (1930, 1933), von Rad (8) (1931), Marburg (9) (1931), Wagner (10) (1932). The upshot of these further cases, Lange considers, prove Schilder's

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contention that fingeragnosia as such may exist, but that there may also be an optic fingeragnosia, constructive fingerapraxia, apractic disorder of finger choice, and fingeraphasia. Lange concludes that fingeragnosia *may be*, but *need not be* accompanied by any one or more of the following features: right-left disorientation, motor, optic or constructive apraxia, sensory, amnestic, or motor aphasia, optic agnosia, agraphia, astereognosis. Right homonymous hemianopsia and the failure of optokinetic nystagmus appear to be constant features (Kroll (11), Lange).

Gerstmann, in his original paper, was inclined to attribute the condition to a lesion in the lower left parietal region, specifitally in the angular gyrus, especially since Wernicke had already assigned to that region the "seat" of "pure" agraphia. Shortly thereafter Hermann and Pötzl (1926) had a somewhat similar patient in whom, however, agraphia stood more in the foreground, and in whom autopsy revealed a lesion in the left angular gyrus. Autopsy in Lange's (1930) case of fingeragnosia with slight sensory and marked amnestic aphasia confirmed the previous findings. In Marburg's (1931) case of fingeragnosia with deep sensibility impairment of the right hand, right-sided hypaesthesia and paresis, and word-finding difficulty but without agraphia, there were two lesions, one in the angular gyrus, the other in the supramarginal gyrus. Marburg, judging from the correspondence between the clinical history and the apparent relative ages of the lesions, ascribed the fingeragnosia to the lesion in the supramarginal gyrus. Lange (1933) reported another case with right-left disorientation, also with lesions in the angular and the supramarginal gyri. He tended to join with Bonhoeffer (12) and with Zutt (13) in ascribing the right-left disorientation to the lesion in the supramarginal gyrus, and the fingeragnosia to the lesion in the angular gyrus.

Klein (14), in reviewing the functions of the pariental lobe, comes to the conclusion that the parieto-occipital convexity represents what one might call a "hand area," i.e., the cortical representation of hand recognition and activity, contributed to by deep sensibility, optic, acoustic and motor mechanisms from adjacent regions. Lange accepts this view, but adds that the fingers would seem to have their special representation in the angular gyrus in its transition to the second

occipital gyrus. According to Klein, Pötzl attributes the function of this region to its special cytoarchitecture, specifically to the sensory visual band of Elliot Smith, and the Gerstmann syndrome to a lesion in the occipital portion of this band.

It is significant that fingeragnosia should be present without other autotopagnostic features. In other words, the fingers have acquired a more highly differentiated and perhaps therefore a more vulnerable place in the *Körperschema* than other portions of the body. The thumb, index and little finger hold distinct positions, the other fingers less so. Schilder (15) reports that most senile patients can still point out the thumb, and Lange states that in fingeragnosia fewer errors are made with the thumb and little finger. The condition is said always to be bilateral, although, when complicated by deep sensibility impairment, it may be more pronounced on the affected side. This feature needs further checking.

Such is the status today of the clinical-anatomopathological problem. As might be expected, the eternal conflict between the localizationists and the non-localizationists has attacked this new problem. Lange (1930) in the first thoroughgoing psychological analysis of a case of fingeragnosia with right-left disorientation, agraphia and acalculia, rejected the concept of a global reduction in the total personality, a concept that Gelb and Goldstein (16) had advanced previously in connection with a case of amnesia for color names. He rejected this concept for Gelb and Goldstein's case also, preferring in both cases to speak of relatively intact personalities, with disorder in a special tool in the service of the personality. This disorder, or basic disturbance, Lange showed to be in the single categorical function of "direction in space," and in the "spatial connections arising therefrom." He showed further that this basic disorder underlay all the features of the syndrome, namely, fingeragnosia, right-left disorientation, agraphia and acalculia. In other words it was not necessary to assume a separate lesion for each one of the features of the syndrome, since they were all only different manifestations of the same basic disorder. In like manner Lange disposes of such generalizations as Goldstein's (17) difficulty in differentiating "figure and background," and van Woerkom's (18) basic difficulty in "abstracting."

Zutt (1932) came to the same conclusion concerning the primary

disorder of "direction in space" in a patient with right-left disorientation constructive apraxia, and pure agraphia but without finger-agnosia. Evidently Lange's hypothesis could be too widely applied.

In a stimulating research on the general motility of aphasic patients, Grünbaum (19) postulated a concrete and abstract activity in "personal space" (*Eigenraum*) and in "outer space" (*Fremdraum*). These distinctions are variable, depending on the task, the degree of conscious planning as opposed to the automatic activity, the mood, general bodily condition, etc. He showed that the automatic activity of healthy people recognized no frontier between the two, and only when conscious attention is necessary to the performance of the task does difficulty arise. Commonly such conscious attention is necessary after damage to the sensory-motor association areas. Wagner (1932) used Grünbaum's conceptions in the explanation of the difficulties in his case of fingeragnosia with deep sensibility impairment, autotopagnosia, apraxia, and aphasia. Lange's modified formulation, based on Grünbaum's postulates, is that the basic difficulty in finger-agnosia, and in its associated features, agraphia, acalculia, right-left disorientation, is the loss of that ability possessed by healthy people to change automatically the hand from a part of the body in "personal space" into a tool or object in the service of the personality in "outer space." This formulation embodies his original conclusion concerning the loss of the function, "direction in space," but gives better definition as applied to this syndrome.

Schilder objects to such general concepts, with the complaint that they add nothing to our understanding. What are needed for the elucidation of the several features of the syndrome are more empirical facts. Lange's contention that such general concepts can throw new light on old facts and new observations, even though these concepts may represent only the personal bias of the observer, will hardly be contested. The perils of the localization doctrine were learned from the aphasia history; natural science has only recently freed itself from that product of over-generalization, the ether. Fortunately the scientist today can be and should be both a localizationist and a non-localizationist. All can agree with Adolf Meyer (20), when he calls for a review in common sense terms of what each patient can and cannot do. If facts of localization or forumulations attempting to

find more basic disturbances underlying empirically discovered defect really conform to the facts, then so much the better.

Most of the cases of fingeragnosia reported to date have resulted from circumscribed vascular damage. Such cases, while by far the most suitable for close study of the syndrome, are relatively less frequent than cases with more far-reaching damage. The following cases are interesting as occurring in (1) the development of a space-occupying mass, and (2) in the subacute stage of lead encephalopathy, respectively, and in the latter for the transient character of the fingeragnosia in comparison with the other features of the syndrome.

Case P. M., male, 49 years old, admitted to the Universitäts Psychiatrische-Nervenklinik, Breslau, on February 27, 1933.

Complaint: Forgetfulness, inability to calculate, difficulty in speaking and writing, dizziness, a heavy feeling in the right leg and a cold feeling in the right arm.

Present Illness: The patient, in the summer of 1932, had felt tired, and complained that his legs stumbled. He began to have so much difficulty in differentiating trees, that he had to give up his work as the foreman of a forestry squad. He sat about the house, moody and listless. Later in the summer he had a generalized convulsion. His condition became gradually worse. Early in January 1933 he experienced difficulty in writing, and by the end of the month could write only his name. Calculation became difficult and he entrusted it to his daughter. Word-finding difficulty appeared. He was confused when in unfamiliar surroundings. Attacks of dizziness, headache, coldness in the right arm, and heaviness in the right leg were other features.

Past History: uneventful, and not contributory to the present illness.

Family History: of no importance.

Direct Examination:

Physical status: Powerful man, in good general condition but looking older than his years, with slight thickening of the arteries; blood pressure 135/75; chest and abdomen normal.

Neurological status showed the following positive findings:

1. Probable diminution of deep sensibility in the right arm and leg.
2. Slightly shuffling gait and right leg slightly spastic.
3. Slight, inconstant tremor in right arm and right leg.

The eyegrounds, visual fields, and tendon reflexes showed no pathological alterations. The cerebrospinal fluid showed a negative Wassermann reaction, no cells, a 1+ Pandy reaction, and a mastic curve with gradually diminishing precipitation, a modified paretic curve. In the x-ray of the skull was seen a lighter area in the left parieto-occipital region. Ventriculogram showed the right ventricle filled with air, but pushed to the right; the left ventricle without air, and a suggestion of a mass lying about the region of the lower horn posteriorly.

The *diagnosis* of a deep-seated tumor seemed most likely. Operation on March 22, 1933, disclosed the tumor as deep-seated and inoperable. A large bone flap was made to give symptomatic relief and to facilitate deep x-ray therapy.

There appeared after operation the following positive neurological findings, which were repeatedly observed up to the end of his series of x-ray treatments in August 1933:

1. Increased tendon reflexes with paresis on the right side.
2. Right hypaesthesia, including deep sensibility, and hypalgesia.
3. Stütz reaction in the right arm.
4. Right homonymous hemianopsia.

He had occasional generalized epileptic attacks, and complained of paraesthesias in the right arm and leg.

More important for our purpose were the mental status and the results of the special examinations. These were carried out both before and after the operation, without any special change from one time to another, and may be summarized as follows:

1. *Mental Status.* He was oriented for place and person, and approximately for time; was willing and cooperative, on good terms with his fellow patients, and in no sense was peculiar on the ward. He experienced subjective difficulty in understanding complicated questions, and in finding the proper words. His attention was poor, although he was aware of the difficulty, and tried to correct it. His general intelligence was average.

Stereognosis was present on the left, but he recognized only three of six objects with the right hand, and even then slowly. He was aware of the difficulty.

Motor Praxis: Face practically without error to verbal commands, also in imitation.

Right hand: very clumsy with the use of objects; generally successful after hesitation and mistrials in performing to order without objects.

Left hand less clumsy with the use of objects but also less successful in performing to order without objects.

Both hands together. Very poor results with verbal orders, either both hands doing the same thing when different acts were called for, or making only confused amorphous movements. Slightly better when actually using objects, but fumbling a good deal and never performing correctly.

Constructive Praxis:

Drawing free hand to order clumsy, but on the whole well done, except for a "quadrangle" which he made as a straight line once, and another time as a triangle, from perseveration. He had difficulty in making two triangles from a quadrangle.

Copy from form: accurate.

Copying diagrams with match sticks: accurate.

Copying with match sticks after the model was removed: only one slight error.

Speech. The patient complained of forgetfulness and of word-finding difficulty.

Spontaneous speech on the whole good, with occasional literal paraphasia.

Repetition good; repeating commands several minutes later, even when he was unable to execute them.

Understanding of spoken words. There was both subjective and objective difficulty in understanding, but he could always be made to understand.

Reading. He recognized letters, numbers, and forms, and crossed them out accurately in the test text. There was great difficulty in reading words, less with single letters and numbers.

Writing.

Spelling was practically impossible except for his name.

Dictation. Very poor, getting stuck on one letter and repeating it or simple combinations with it to quite different dictated words. He could write his name, occasionally omitting one "l" in the surname. He had better success with dictated numbers than with words. He was annoyed at his poor showing.

Copy. Fairly well performed; occasional leaving out of a letter and reading the results wrongly. At first he was interested in finding out the sense, and from the sense hastily writing with only a glance at the model. Later he gave up trying to discover the sense and copied letter for letter automatically, with just as good a result as before. Copy of numbers was accurate although he read the result wrongly.

Optic Gnosis. He recognized all test objects; identified "red," called blue "green." He matched only those shades which were practically identical, especially passing over the lighter shades.

Calculation. Practically impossible, even with the simplest problems; but then, at times, he would suddenly come out in a mechanical fashion with a formula learned in school with the proper result. He counted forward and backward from one to ten, but beginning with a larger number made the task impossible.

Autotopognosia: The patient was unsure of his answers, and carried out orders only after a long pause:

"Show your elbow."	Hunts on his fingers, then +.
"Show your ear."	+
"Show your calf."	+
"Show your upper arm."	Repeats the command several times, then points to his forearm.

Music. In general he recognized higher and lower tones, but he was unable to tell how many notes were played at once. He could sing to an accompaniment, but was unable to carry on after the accompaniment stopped.

Right-left orientation:

Of his own body:

"Show the left hand."	+
"Show the right leg."	+
"Show the right hand."	+
"Show the left leg."	+. All answers were given only after a long pause and with uncertainty.

"Put your right hand on your left ear."	No movement.
"Repeat."	"Left hand . . . . right hand on right ear?" Finally repeats properly the command but could not perform it. Several minutes later he could repeat the command correctly, but was unable to perform it. Finally pointed to his left ear, seemed confused. When shown how to do it, he at first reversed the arms, then did it correctly.

The examiner sat facing the patient, while performing movements which he was to imitate:

"Right hand on right eye."	Left hand on left eye.
"Right hand on left ear."	Left hand on right ear.
"Left hand on right ear."	Left hand on left ear, the right hand on right ear, then completely confused.
"Right hand on nose."	+
"Right hand on right ear."	+
"Left hand on right ear."	Right hand on right ear.
"Right hand on left eye."	Left hand on right eye.
("What's wrong?")	Right hand on right eye.
("What's wrong now?")	+
"Right fist on head."	Right fist on forehead, then +
"Right hand on left eye."	+
Fingergnosis: 1. Fingerpointing:	
"Show your thumb."	+ after deliberation.
"Show your middle finger."	+, but unsure.
"Show your index finger."	"Can't do it," confused.
"Show your little finger."	+
"Show your index finger."	First +, then thumb.
"Show your ring finger."	"Don't know that name."
"Show your middle finger."	+
"Show your index finger."	Thumb, then +
"Show your thumb."	Index, then +
"Show your middle finger."	Ring finger, then +
"Show your little finger."	Thumb, then +
"Show your index finger."	+
"Show your thumb."	+
"Show your little finger."	+.

All performances were made only after deliberation.

2. The examiner showed his own hand and pointed out fingers. The patient was to indicate the same finger on his own hand:

ii — +	v — +	v — +
iii — +	ii — +	i — +
i — +	iii — +	iv — +

This was much better performed than the preceding test, but poorly unless the examiner sat alongside the patient facing in the same direction.

3. He was shown a drawing of a hand, and was told to indicate on it the same finger as the examiner pointed out on his (the patient's) hand:

This test led to more uncertainty than the preceding one (2).

4. The patient was to indicate on his own hand the finger pointed out on the drawing.

This was done promptly after the initial difficulty in understanding the task was overcome.

5. Without benefit of visual control the patient was to point out on the drawing the same finger as the one of his own that the examiner moved.

This was promptly done, with only one mistake: for iii he pointed to iv.

The tests show fingeragnosia not influenced by constructive apraxia, optic agnosia, or astereognosis. The performance is notable for the special difficulty with the thumbs and little finger.

Summary: A rapidly progressive brain tumor deep in the left hemisphere in the parieto-occipital region, with principal features of right-sided sensory-motor disorder with hemianopsia, and marked acalculia and "pure" agraphia. Fingeragnosia and right-left disorientation (and autotopagnosia?) were discovered only on systematic examination. Slight constructive, and more marked motor apraxia, slight optic agnosia, and slight sensory-motor-amnestic aphasia, alexia and amusia complicated the picture. In view of the etiology, the extent of the involvement can cause no surprise.

The fingeragnosia appeared to be uninfluenced by these complications, unless perhaps by the apractic difficulties. The protocol does not permit a definite statement on this score. Complicating the tasks demanded of the fingers by right-left choice brought greater uncertainty.

Case E. H. Male, born July 14, 1902, a welder in a steel mill, was admitted to the Universitäts Psychiatrische-Nervenklinik, Breslau on February 9, 1932.

Complaint. Continuous headache, dizziness, trembling of the hands, pains in the abdomen and legs, inability to write properly, anxiety "dreams," and depression.

Present illness. The patient had been employed as a welder, working with lead since 1924. In 1929 he felt weak, his appetite failed, and he complained of headache. Examination disclosed a lead line on the gums. He intermittently took "cures," and worked until 1931, when, with a general increase in all his symptoms, he had his first attack of unconsciousness, with a generalized convulsion, biting the tongue. At the same time he noticed that his vision was very poor, and deafness of the right ear appeared. He was finally brought to the hospital.

Examination showed the following positive findings:

(1) Lead line on the gums, spastic colon, marked secondary anemia, and basophilia.

(2) Bilateral optic atrophy, the result of neuritis; complete right homonymous hemianopsia; poor facial mimicry; slight right facial and right radial paresis; tremor of the tongue and of the extended fingers and hands; somewhat uncertain movement in the heel-knee test; spontaneous pains in the legs; in the cerebrospinal fluid 4 cells and + Pandy reaction; Jacksonian attacks beginning in the right arm, spreading to the right leg, then to the left side and followed by an anxious delirious state.

(3) Gerstmann's syndrome: fingeragnosia, mild; right-left disorientation, mild; marked acalculia and agraphia.

(4) Difficulty in carrying out complicated movements with the hands (optic apraxia).

(5) Word-finding difficulty and paraphasia, marked.

(6) Difficulty in color recognition.

(7) Memory difficulty for complicated tasks, and slow thinking.

By contrast, he was well oriented for time, place, persons; cooperative, with normal attention and average intelligence.

Under treatment directed toward the chronic lead intoxication he soon showed considerable improvement in all these features, and was discharged from the hospital. He was examined again in 1933 and 1935 with findings indicating that a rather stationary condition of defect has been reached. The final examination shows the following:

The general condition is one of listlessness, with occasional moments of excitability. He takes an interest in politics, and the news of the day, but can give only a very inadequate and superficial account of events. There are no gross mood swings. He cannot work. He spends a good deal of his time listening to the radio.

General physical status: He has gained weight, looks quite well, the blood picture is normal, there are no gastrointestinal complaints, and the lead line on the gums has disappeared.

Neurological status. The sense of smell is diminished; the right corner of the mouth droops, the tongue is unsteady; there is tremor of the hands. With eyes closed he tends to walk to the right, but there is no ataxia. With rapid pronation-supination movements of the forearms there is marked associated lateral movement of the lower jaw. Sensory examination is normal. There is complete right homonymous hemianopsia and bilateral optic atrophy with reduced vision.

Special tests:

Fingeragnosia. The patient names and points out correctly all fingers of either hand on himself and on the examiner. He names and points out on a drawing the finger indicated on himself, and vice versa. He indicates on the drawing and names the finger moved by the examiner. With both hands behind his back he executes similar tests accurately, but experiences more subjective difficulty. Even with the hands in the position of the "Japanese Illusion" he makes only four errors in ten trials, complicated by right-left discrimination.

He fares somewhat worse when the orders are given rapidly, doubtless as a result of a non-specific thinking and retention difficulty.

There is no fingeragnosia or fingeraphasia.

Fingerapraxia. The patient moves all fingers freely, singly and together; he makes complicated movements and assumes complicated postures accurately, without hesitation or fumbling.

There is no fingerapraxia, optic, constructive or motor.

Right-left orientation. The patient is oriented for right and left with regard to his own body as well as objects in the room, although he is sometimes uncertain; also for objects before, behind, above, below. On the other hand, complicated hand movements directed to parts of his body, involving right-left discrimination, are sometimes difficult, uncertain or wrongly made. Imitation of movements made by the examiner facing the patient are generally mirror images, whereas imitation of such movements made by the examiner standing behind him and facing a mirror are accurately and quickly done.

There is no static right-left disorientation, but kinetic orientation is disturbed ("Praktognosia" of Grünbaüm).

Apraxia: There is no motor apraxia, and constructive apraxia is shown only for complicated productions.

Color recognition accurate; there is no other evidence pointing to optic agnosia.

Calculation: The patient experiences difficulty even with simple problems, especially when the actions have to be carried out without looking at the written problem. Even with looking, errors are frequent.

Writing. Both spontaneous writing and the copying of words, sentences and numbers are poor, but the former is much worse. He leaves out words from sentences, as well as spelling incorrectly, and frequently gives up the task as impossible. He writes his name properly, and keeps to a straight line (which was formerly impossible).

Speech. He experiences some word-finding difficulty with occasional paraphasic utterance. At times also there is some difficulty in understanding spoken words, but always he can be made to understand the tests.

Reading. He reads poorly, haltingly, separating polysyllabic words into their syllables, and gives a poor account of what he has read. He reads numbers poorly.

Summary: Chronic lead intoxication with definite evidences of lead encephalopathy, with development as a transient feature in the subacute stage, of the full-fledged Gerstmann syndrome, and complicated by optic apraxia, paraphasia, alexia, difficulty in color recognition, and general memory and thinking difficulty. Under treatment the fingeragnosia and the static right-left disorientation disappeared completely leaving its companions, acalculia, agraphia, and slow uncertain kinetic right-left disorientation as permanent features. Slight constructive apraxia, aphasia, and alexia also remained.

As with the previous case the sureness in performance of the fingers was impaired by the necessity of making right-left choice, and by a rapid sequence of orders.

The patient suffered a general reduction in efficiency due to the thinking and memory difficulties, but in addition there was the impairment of the special "tools" as noted.

SUMMARY

(1) Two cases illustrating the Gerstmann syndrome of fingeragnosia, right-left disorientation, agraphia, acalculia, and right homonymous hemianopisa are presented. Slight constructive apraxia was found in both cases. Additional complicating features were aphasic, apractic, alectic, and opticagnostic. Autotopognosia was intact in the second and very little impaired in the first case in spite of one-sided sensory impairment.

(2) The cases are interesting as occurring as (1) a permanent development in a brain tumor case, and (2) a transient feature in chronic lead encephalopathy. In the second case the close coincidence of fingeragnosia and static right-left disorientation and their simultaneous disappearance under treatment, together with the greater difficulty in fingergnosis when complicated by right-left choice (especially when kinetic right-left orientation was necessary) point to a close common factor.

(3) Both cases can serve as illustrations of the validity of Lange's formulation of the basic difficulty as one of failure in the automatic ability to change the hand from a part of the body in "personal space" to a tool in the service of the personality in "outer space." This formulation however offers no explanation of the complicating features.

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RESEARCHES ON TETANUS

IV. Some Historical Notes on Tetanus and Commentaries Thereon[1]

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We have confined ourselves in these notes to a presentation of the views, on the nature of tetanus, of a limited number of writers of the past century and a half. A more exhaustive survey of the papers written during this time on this subject could not be given short of inflicting on the reader a large treatise encumbered by a mass of details, many of which have lost the significance that once attached to them and are now of interest solely to students of the rise and fall of errors in the history of disease. Fifty years ago, Behring remarked, in one of his notable papers, that the literature of tetanus is of such vast extent that it is almost incapable of being surveyed ("fast unübersehbar"). Always in times of war the flood of papers on the disease runs high. Rose (45) tells us, with a touch of humor, that during and after the wars of the latter part of the eighteenth and the early years of the nineteenth century it became quite the mode to write a "thesis" on tetanus ("es wurde zur Modethema"). Since Behring's time the flow of papers has increased rather than lessened.

The literature of the world war and that appearing since its termination has established more firmly than ever the prophylactic value of the antitetanic serum, but has also shown its very doubtful value as a curative agent, once the toxin has been distributed throughout the body and no longer remains confined in its action to the segment where it originated. The more recent papers by clinicians are of importance in emphasizing the more than doubtful value of injecting the antitetanic serum into the subarachnoid spaces, with either a prophy-

[1] A grant from the Carnegie Corporation of New York has made it possible for the authors to carry on a series of investigations on tetanus.

lactic or curative purpose in mind. It has long been known that when large amounts of this serum are injected into these spaces it is rapidly and almost completely transferred to the general circulation (44); also, that when excessive quantities are injected into a vein, only mere traces of it, in comparison with what was injected, are found in the cerebrospinal fluid. So, too, when a fatal dose of the deadly toxin is injected into the subarachnoid space, it soon finds its way into the blood stream and induces a descending tetanus only, unless the pial membrane has been designedly or accidentally injured, in which event, the consequent more or less localized poisoning of the spinal cord will evoke prior symptoms of a character not seen in descending tetanus.

Many therapeutic procedures have been discarded within the past thirty years; among these may be named the direct and very dangerous injection of the antitetanic serum into the substance of the brain, and its surgically practicable but not truly beneficial injection into a large nerve like the sciatic, or into branches of the axillary or brachial plexuses. All of these futile attempts to counteract the action of the toxin were based on the theory that tetanus is solely a disease of the central nervous system and that its toxin is carried by way of the peripheral nerves to central nuclei. It is gratifying to learn that they have been relegated to that *limbus errorum* to which the practice of amputating fingers, hands, arms or legs, and of transecting or violently stretching the nerves of a tetanized extremity, at the first outbreak of tetanus, have long been consigned. The amputation of limbs[2] and

[2] This practice has been continued, unfortunately, almost up to our time. One of the leading authorities on tetanus, Rose, still advocated it in 1897, in the second edition of his very important and extensive treatise on tetanus. He did this, however, with reservations, but was convinced that amputations performed in the very early stages of tetanus prevented death. We are firmly of the opinion that a human being with tetanus who has escaped death after a mutilating operation of this nature would not, under the circumstances, have died from the disease had the surgeon not intervened. This surgical procedure has been tested in too many experiments on animals, with entirely negative results, at various intervals after toxin injections, or, after infection with *Cl. tetani*, to warrant the belief that it can ever be of service in the treatment of a tetanic human being. In experiments on animals the amount of toxin injected, the length of the period of incubation, the intensity and progress of the tetanic symptoms, can all be varied at will, but even under the most favorable conditions the life of an animal cannot be saved after the injection of a lethal dose of the toxin unless the amputation is done within an hour or so after the injection.

transection of nerves to check the progress of tetanus seemed rational enough to justify their trial a century ago, and the same may charitably be said for the more recent practice of intracerebral, intrarachidian and intraneural injections of antitoxic serum, as well as the use of an impractical and dangerous drug such as magnesium sulphate. The clinicians who made use of these agents were misled by a too ready acceptance of the favorable reports of experimental scientists on their therapeutic value. In view of the fact, however, that the employment of such physical and chemical agents and of many others that have not been named, has been entirely unable to survive the stern arbitrament of actual trial on human beings with tetanus, it is indeed surprising to learn that their enforced abandonment has not sufficed, as it should have done, to raise doubts in the minds of more recent writers, in respect to the validity of the theories that fathered them.

While the literature on tetanus of the present day is thus of significance in respect to the usefulness of antitoxic serum and in demonstrating the uselessnesso f many methods that have been hitherto tried for the purpose of checking the progress of the disease, it throws, in our opinion, no more light on the true nature of the disease than if it had appeared a century ago.

About forty years ago, when the now accepted purely central theory came to be regarded as irrefutable, mainly in consequence of the support it received from experimental scientists, a number of writers raised objections to it, on the ground that it fails to account in a satisfactory manner for many of the features of the disease. No theory of tetanus can hope to survive, whose tenets cannot be made to square with observations at the bedside. We would lay particular emphasis on the clinical significance of our belief that the toxin of the disease acts directly and in a very significant manner on all voluntary muscles of the body, irrespective of the pathway by which it reaches them; that this action is a graded one, varying in degree with the number of "muscle units" that have responded to it in accordance with the "all or none" law, if we may assume this to hold in the case; that the toxin elicits at first, a hardly demonstrable stiffness of the muscles, which passes gradually into the well known extreme stage of an unyielding rigid contracture, when the affected muscles can no longer respond to voluntary impulses and no longer become flaccid after sectioning their motor nerves. We have every reason to believe that

every stage of contracture, inclusive of the terminal one, is due, not to an action of the toxin on central motor nuclei, but to its direct action on the muscles themselves, as was pointed out in experiments reported in our Paper III. Further proof of this statement will be offered in Paper V. We would merely remark in passing that our theory of the true cause and nature of this contracture of voluntary muscles squares with what may be seen at the bedside of an individual dying from descending tetanus. He who has carefully noted the symptoms in the case of a vigorous young man during the last twenty-four hours of life, when the abdominal muscles are of board-like hardness, when the diaphragm and all of the essential muscles of respiration are entirely unequal to their task of maintaining normal respiration because they have likewise attained a state of terminal rigidity, and has observed that the increasingly feeble respirations are kept up only by the extreme efforts of the accessory muscles of respiration that have not yet become entirely rigid, cannot escape the conviction that he is seeing a man being slowly suffocated, and this, not because the respiratory and other central motor cells have been poisoned, or, because of secondary pulmonary complications, but in consequence of the direct action of the toxin on all of the muscles that are either directly or indirectly concerned with respiration. In instances of head tetanus with long continued laryngeal spasms the cause of death is also primarily of peripheral and not of central nature. The terminal symptoms in individuals dying from suffocation during tetanus have been described thousands of times in the history of the disease, but always without suspecting that their cause is to be found in the peripherally evoked rigidity of the respiratory muscles rather than in hyperexcited central nuclei.

It is not our purpose to go into details at this point in connection with death by asphyxia in the various stages of the disease, or to give here the results of our autopsy findings in dogs and sheep when slow suffocation was the terminal event. Rose devotes much space to this cause of death and the state of the lungs and heart and other organs as disclosed by autopsy.[3] He points out that a fatal asphyxia may occur even after, or during one or two violent spasms, or "shocks,"

[3] See his paper listed in the Bibliography: "Der Starrkrampf beim Menschen," 1897, pages 59 to 62, 107 and 108, and 146 to 148.

involving the truncal muscles [his "Gewaltstösse," or "Stickstösse"]. Such spasms may last for fifteen minutes and terminate fatally. In these instances efferent impulses due to a central action of the toxin are probably superimposed on the locally poisoned, but not as yet completely rigid muscles involved in respiration. It should be borne in mind that Rose, despite his appreciation of the dire significance of long continued muscle contractures in inducing asphyxia, never for a moment believed that such contractures of voluntary muscles could be due to a direct action of the tetanus toxin on them and their neural terminals.

The reader may well bear in mind, in connection with the statements that have just been made, that the antitetanic serum now at our disposal is powerless to prevent the appearance, or to retard the progress of the muscle contractures, once the muscles have absorbed, during the period of incubation, more than an ineffective minimal amount of the toxin.

In cases of severe tetanus such as we had in mind in writing the preceding sentences, it is the usual practice to make use of such hypnotics as avertin, veronal or sodium luminal in order to reduce the number of reflex spasms or convulsions. We ourselves have recently noted that even when the patient was kept for many hours at a time so deeply under the influence of these agents that all ordinary reflexes were abolished, the rigidity of the abdominal muscles, those of the neck and back, and those essential to respiration did not relax in the later stages of the disease. The anaesthetized and unconscious individual did not breathe any more easily and still struggled for air, insufficiently supplied through the agency of the accessory muscles of respiration. Death ensued as a consequence of slow suffocation, "the terminal event apparently being a dilatation of the heart," in the words of the clinical record. Early writers on tetanus had experiences similar to ours when chloroform was carefully used within the limits of safety as an antispasmodic at a time when the powerful anesthetic action of this drug first became generally known.

It will be shown in a later paper on the effects of the direct injection of the toxin into the spinal cord, that all of the very striking *reflex* spasms evoked by this central form of poisoning disappear at once after a few whiffs of ether, to return, however, after its effects have

worn off. But, even deep etherization, short of inducing death, is powerless to undo the rigid contractures of muscles that have been poisoned by subcutaneous, intramuscular or intravenous administration of the toxin. There is, then, a striking contrast in the ease with which anaesthetics and hypnotics inhibit reflex spasms and convulsions of central provenience and the very limited power of these drugs to undo the peripherally induced contractures of which we have been speaking.

The following historical facts and commentaries are intended to serve as an introduction to our forthcoming papers V and VI, in which will be given (1) further experimental work in proof of the peripheral action of the toxin and the clinical significance of this action; (2) our experiments on the purely central type of symptoms illustrated by intraspinal injections; and (3) conclusions on the relation in time, to each other, of the peripherally and centrally caused symptoms of the disease.

Two opposing views in regard to the nature of tetanus are encountered in studying only a limited number of the innumerable descriptions of its protean manifestations that have appeared within the past two centuries. Belief in the theory that tetanus is solely a disease of the central nervous system, has a more ancient and a far more distinguished lineage than has any modification of it hitherto offered by its opponents. Enunciated many centuries ago as accounting in the most obvious and logical manner for the events occurring at the bedside, it has received within the past fifty years the practically unanimous support of a large number of experienced and influential bacteriologists, pathologists, physiologists and pharmacologists. The researches that were carried out by these experimentalists with the causative agent of the disease—the toxin of *clostridium tetani*—assumed an importance that enabled the earlier clinical belief, permissible enough in its day, to acquire its present status of an irrefutable theory.

A century ago, Thomas B. Curling, a young assistant surgeon to the London Hospital and lecturer on morbid anatomy, wrote his well known essay entitled "A Treatise on Tetanus," for which the Jacksonian Prize for the year 1834 was awarded. In the section of his essay entitled "Theory of Tetanus," Curling remarks, "That the

spinal marrow is the seat of diseased action in tetanus, is in truth by no means a modern opinion, having been maintained by Galen, and adopted by Fernelius, Willis, Hoffman, and Lieutaud." It may perhaps interest the reader if we select Curling as representing the views of his predecessors and contemporaries in respect to the nature of the disease, more especially since he is representative of that large number of clinicians as well as of experimentalists who have confined themselves to a study of the purely centrally induced symptoms of the disease without paying due attention to its local forms.

After a careful study of his own cases of tetanus and his autopsy records and numerous cases of the disease as described by others (128 cases in all), Curling says, "I am induced to infer:

"1. That tetanus is a functional disease of the nervous system, that is to say, a disease unaccompanied with any perceptible lesion of structure, the nature of which, although essentially distinct from inflammation, is completely unknown. There are, therefore, no morbid changes peculiar to tetanus, and by which it can be recognized.

"2. That the seat of this peculiar morbid action, termed *tetanic irritation*, is the *tractus motorius*, on either side, wholly or in part, the superior being the portion most generally affected.

"3. That the result of tetanic irritation in the *tractus motorius*, or medulla, is a supply to the muscles of a stimulus to abnormal action, which, although limited to the muscles subservient to the will, is, nevertheless, totally without its control."

The reader should note that the word *medulla* in this paragraph is equivalent to *medulla spinalis*. In connection with this paragraph we may cite a few paragraphs from earlier pages of the essay. Thus, on page 86 Curling remarks, "Tetanus then appears to consist in a peculiar morbid action in the *tractus motorius*, the intimate nature of which is altogether beyond our comprehension." And again, "The result of tetanic excitement in the *tractus motorius*, however caused, is an extraordinary supply to the voluntary muscles of a stimulus to action totally independent of volition, which, although supplied in increased force at varying intervals, *is so continued as to render the contractions permanent*;[4] and it is remarkable for how great a length of time the action of the muscles is prolonged, without occasioning that

[4] Italics ours.

distressing sense of lassitude ordinarily consequent upon muscular exertion, when induced by the stimulus of the will. But although the spasms in tetanus are in no degree subjected to voluntary control, yet it is curious that in sleep, when volition is in abeyance, the excitement to action resulting from the morbid irritation is likewise withheld."

We have cited this long paragraph primarily to show that Curling believed that the repeated and violent central stimulation of muscles could "render the contractions permanent." This opinion, which we hold to be entirely erroneous, is held even by modern experimenters, such as Liljestrand and Magnus, who believe that the permanent rigidity of muscles so frequently seen both in clinical cases and in experimental work is maintained by a steady discharge of efferent impulses from hyperexcitable centers stimulated by a constant inflow of proprioceptive and other types of afferent impulses.

In paragraph 4 Curling deals with irritations of the medulla [spinalis] that "may be caused by a wound, cold, or any other source." An occurrence of this nature, he holds, can induce that frequently appearing variety of the disease long known as idiopathic tetanus, in contradistinction to the usual traumatic tetanus. Here, as in his chapter on tetanus neonatorum, he could not rise above the erroneous beliefs of his day.

"5. That, in pure traumatic tetanus, the primary impression is confined for an indefinite time to the nerves of the part injured, being transmitted at some subsequent period to the medulla [spinalis], and thus exciting the disease."

If we substitute *tetanus toxin* for Curling's "primary impression" and *period of incubation* for his "confinement of action for an indefinite time to the nerves of the part injured" we shall have phrased his thoughts in the language of our day.

"6. That when tetanic irritation is once fully excited in the medulla [spinalis], which is made manifest by spasmodic contractions in the muscles, the disease is independent of the exciting cause, and does not cease upon its removal."

The citations that we have here given from Curling's essay show that his views and, we may add, that of others both before and after his time, practically coincide with the orthodox opinion of our day

that tetanus is solely a "functional disease" of the central nervous system. The essay was translated into German and the surgeon Rose, of Zurich and later of Berlin, who certainly had a wider experience with tetanus than any other of his European contemporaries, remarks, that "Curling's reflex theory" so influenced Romberg and Friedrich and others that their writings became mainly responsible for the acceptance and extension of Curling's views in Germany. We have found it more convenient to discuss Rose's own opinions on tetanus in a later section.

We need not here give the long list of writers, containing many of the most distinguished names of medicine, of pathology, and of the physiological sciences, whose clinical observations and whose deductions from experimental work, so often based on unwarranted assumptions, finally led to the adoption of our present dominant theory of tetanus. The work of many of these writers has already been mentioned in our earlier papers and that of others will be analyzed in later ones of the series.

IDEAS OF OPPONENTS OF THE THEORY THAT TETANUS IS SOLELY A DISEASE OF THE CENTRAL NERVOUS SYSTEM

The unitary or central neural hypothesis met with opposition from various quarters as early as the latter part of the eighteenth century. A more extended examination of the literature would no doubt disclose earlier instances of dissatisfaction with the theory. These critics very properly asserted that the adherents of the "purely reflex theory" had not paid sufficient attention to the frequent appearance of rigid contractures of muscles in the region of the primary seat of the infection, or to the fact that these local contractures can occur before reflex jerks or convulsions make their appearance. Thus, Plenk, in 1788, made a sharp distinction between a "species of cramp (*Krämpfung*) which may attack the entire body, and may be seen especially in the muscles attached to the spinal column, and may persist continuously for some days, and convulsive seizures," and goes on to say, "therefore one must not confuse true tetanus with convulsive contractures which are constantly changing and which last only for a short time or which attack only certain parts of the body." Rose says that Plenk drew his deductions from the acute forms of tetanus,

while Romberg and Friedrich, who, as already stated, were mainly responsible for the acceptance of Curling's views in Germany, based their conclusions in regard to the central nature of the disease upon such varieties of tetanus as were then called the "mild rheumatic forms, which are essentially characterized by intermittent convulsive seizures."

How widely opinions differed in regard to the matter under discussion, in the days of which we are writing, is shown by the opinion expressed by the Norwegian professor Heiberg (1861), that local tetanus in reality is quite independent of any central influence and is due to the direct action of the toxin on the muscles themselves. In the following summary, as given in the only one of his papers known to us, Heiberg gives his theory of the pathogeny of tetanus as based solely on his clinical observations. He asserts that:

"Tetanus is not a nervous disease but a disease of the blood or a blood-poisoning which localizes itself in the muscles.

"This localization reveals itself as a degeneration or metamorphosis of muscular tissue, in all probability due to a change or lowered function of the trophic innervation.

"An immediate consequence is shortening or stiffening of the muscles, the tetanus never attaining the status of cramps but rather of contraction.

"Reflex cramps occur, but these are merely casual and not essential to this disease.

"We must therefore treat the trophic innervation at the site of the disease and further employ such means as will render the waste material harmless if not destroy it; or at least promote its conversion and absorption."

The writings of the surgeon Rose of Zurich, a contemporary of Heiberg, are well known to all students of the history of tetanus, and particularly to those whose chief concern is with the clinical aspects of the disease. It was he who introduced the term "head or cephalic tetanus" (*Kopftetanus*) as a designation for that form of local or partial tetanus that appears when the seat of the infection with *clostridium tetani* is on any part of the face or the head. It must not be confused with the term "cerebral tetanus," employed by Roux and Borrel to describe the results of their *intracerebral* injections of

the toxin into rabbits, guinea-pigs, and other animals. This experimentally induced variety of tetanus is never seen in the natural disease; *it is purely a product of the laboratory.* In rabbits and guinea-pigs intracerebral injections lead to "excitation, crises convulsives intermittentes, troubles moteurs, polyurie, etc. Les symptômes diffèrent suivant la région injectée" (17). In the rat convulsive crises are absent but psychic manifestations predominate. In place of the ordinary permanent contractures of tetanus, Roux and Borrel find "in cerebral tetanus only signs of central excitation, of epileptiform crises, of polyuria and motor disturbances that give to this 'maladie' a physiognomy which is easily recognized."

We may interrupt our narrative at this point long enough to give a brief account of some further work of these authors on the curative action of the antitetanic serum. They were convinced adherents of the central theory of tetanus and stated in the most positive terms their belief that all of the symptoms of the disease result from the fixation of the toxin by motor cells of the central nervous system. Except for the reason that it was thought advisable to speak of their cerebral tetanus in this part of our paper, in connection with the purely local or so-called head tetanus of Rose, it would have been more in order to review their work in the preceding section. These authors, like their contemporaries, were well aware of the fact that antitetanic serum is capable of neutralizing toxin that is encountered in the circulating blood, but they were convinced that "il est impuissant contre le poison arrivé déjà aux éléments nerveux." They go on to say: "C'est pourquoi, dans le tétanos déclaré, il échoue si souvent. Au moment où on l'emploie, une partie de la toxine est déjà adhérente aux cellules nerveuses; l'antitoxine neutralise bien le poison qui circule encore, mais elle n'atteint pas celui qui est fixé aux éléments de la moelle épinière. Elle limite l'empoisonnement. Si celui-ci est trop avancé, la maladie suivra son cours, car la toxine diffusera de cellule nerveuse à cellule nerveuse à l'abri de l'antidote.

"S'il en est ainsi, ce n'est pas dans le sang des tétaniques qu'il faut accumuler l'antitoxine pour les guérir, il faut la mettre là même où progresse la toxine, et préserver les portions vitales de la moelle avant qu'elles soient atteintes."

They received excellent support for their theory by injecting the

antitoxic serum into the cerebral hemispheres of guinea-pigs, twenty-four hours after subcutaneous injection of the toxin into one hind leg. The lethal dose used was of the order that caused the first appearance of rigidity in the injected leg in 24 hours and led to death in about 72 hours. By injecting about 0.125 cc. of their antitoxin into each of the two hemispheres of a guinea-pig poisoned by the stated amount of toxin they were able to prevent death in the great majority of the animals. They took the precaution, however, to protect themselves against the charge of having rashly advised the use of this method as a curative one in human tetanus, by saying that experiments should first be made on larger animals, such as horses and sheep, before this step is taken.

It is to be regretted that no attention was paid to this guarded statement of Roux and Borrel. Blumenthal and Jacob and Fonseca did not obtain equally good results with the intracerebral method of administering antitoxin, but v. Török found it to be superior, in saving lives of guinea-pigs and rabbits, after the subcutaneous administration of a lethal dose of toxin, to the subcutaneous or intravenous method of administering the antitoxin. French surgeons, however, began immediately to apply the method in human cases of tetanus, and thereupon it was extensively employed in many cases by surgeons everywhere. Kocher seems to have been the first to inject the antitoxin directly into the lateral ventricles of the brain. We have not space here to analyze the clinical reports of the many series of cases in which this method was applied so often with disastrous results.[5] It soon became evident that the intracerebral or intraventricular method of injecting antitoxic serum was not only accompanied with danger but was of more than doubtful value in saving the lives of tetanic patients.

In the light of the knowledge now at our disposal it is not difficult to show why Roux and Borrel were entirely mistaken in believing that their intracerebral injections of antitoxic serum saved the lives of their tetanized guinea-pigs because it was thereby enabled to come

[5] The reader who cares to pursue the subject further will find a rather full account up to 1914 in Carl Permin's paper, pages 50 and 54 *et seq.*, and earlier accounts up to 1900 by v. Török, of reports by many surgeons of their experiences with the method.

into contact with and neutralize the toxin that was supposedly bound by the central nervous system. There is not the slightest evidence to show that any toxin was present in this system at the time when the antitoxic serum was injected into the cerebral hemispheres. They were unaware of the fact that the antitoxic serum thus injected passes immediately but gradually from the tissues of the brain into the blood stream, where it promptly neutralizes the toxin that has likewise slowly entered the blood stream from the injected area. It is also well known that the passage of subcutaneously injected toxin into the blood stream, by absorbing lymphatic networks, requires fully three days for its complete removal from the injected area. In the experiments of Roux and Borrel the cerebrally injected antitoxin and the subcutaneously injected toxin, therefore, met each other in the blood stream, and it is not surprising that under the circumstances the greater number of their animals survived the otherwise fatal action of the minimal lethal dose of the toxin.

Roux and Borrel should have tested their method of intracerebral injections of antitoxic serum in instances of head tetanus—a form of local tetanus that is so easily induced in the four-footed animals—by injecting the toxin under the skin of the face. Twenty-four hours after injection of a lethal dose of the toxin, when rigidity of the facial muscles and trismus had begun to appear, they should have injected their antitoxin into the cerebral hemispheres. They would undoubtedly now also have saved the lives of a large proportion of their animals but they would have found that they could not prevent the complete rigidity of the head muscles in such instances of head tetanus; any more than they could prevent the appearance of muscular rigidity in the hind legs of guinea-pigs in those of their experiments that have been subjected to our criticism. It is believed, in accordance with the central theory that, in experimentally induced head tetanus, as also in the analogous clinical variety of the disease, the affected muscles become rigid and pass into contracture, because the toxin has ascended the motor cerebral nerves and has reached the controlling centers of the muscles involved; and it is evident that if intracerebrally injected antitoxin cannot hinder the full development of rigidity in the head muscles, in the experiment under consideration, it could not have met and counteracted the supposedly centrally lo-

cated toxin, as was thought to be the case by Roux and Borrel and v. Török. Certainly, in experiments with head tetanus such as we have outlined and concerning whose outcome we entertain no doubt, the intracerebrally injected antitoxin should have reached the poisoned nuclei of the cerebral motor nerves, in accordance with the central theory, and should have stayed the muscle contractures that are supposedly initiated and maintained by these poisoned centers. The only effect that intracerebral injections of antitoxin could possibly have in experiments of this kind is to influence the reflex effects of the central poisoning, assuming that this is not already in evidence at the time when such injections were made. Fortunately, the method of using intracerebral injections of antitoxic serum, with the purpose of staying the whole course of human tetanus, is no longer employed in our day. It is to be regretted that it was ever tried on human beings, founded as it was on the inadmissible theory on which the experiments of Roux and Borrel and v. Török were based.

We may conclude our remarks on this therapeutic procedure, which has now become a matter of historical interest only, by saying that in our opinion the method of injecting antitetanic serum into the subarachnoid spaces of the lumbar cord—a method that is still so widely employed in our hospitals today—is equally as unnecessary and equally as futile as a *curative* measure, although devoid of the danger to life that was inherent in the intracerebral method. And it is surely superfluous to remark that no one should inflict this method on a patient, in the mistaken belief that it is of greater *prophylactic* service than an intravenous injection of an equal amount of the serum.

Rose had the opportunity of studying many cases of tetanus of various types, nearly 100 in all, according to Axhausen, and he deserves the greatest credit for insisting on the importance of the permanent rigidity of an extremity, or of certain groups of muscles in other parts of the body, that persists as such in the intervals between convulsive seizures. He held that this state of more or less permanent rigidity is the most characteristic feature of the disease and is that symptom above all others that should be regarded as the most important criterion in the making of a differential diagnosis, and remarks that the ancients also held this opinion. He pointed out that

his contemporaries and successors had often mistaken tetanus for certain other forms of disease, such as "meningitis spinalis," "tumor medullae," fracture of the skull with hemorrhage into the brain, extensive inflammatory conditions of the mouth and other pathological states that may simulate trismus. Rose must also be given great credit for stressing the importance of the fact that reflex excitability, so often, definitely makes its appearance only in the later stages of the disease. Since this point is of fundamental importance we may translate a few passages from his systematic exposition (45) in which the relation of the symptom to muscular rigidity is discussed. "It appears furthermore that typical tetanus is not characterized by such convulsive attacks [*Anfälle*] but by muscular rigidity which may persist until death occurs. Traumatic tetanus often runs its course until death without convulsions." "While in strychnine poisoning reflex excitability appears from the very first as the chief symptom, it makes its appearance for the first time in our later or third stage of tetanus and is therefore often completely lacking to the last. It is therefore quite wrong to set up strychnine poisoning as a type to which tetanus conforms.". . ."After we had learned to know tetanus in its true form as a disease that manifests itself in its first stage as muscular rigidity and then passes on to a third stage, with tonic jerks which may become chronic, we discussed *two abnormal types that are associated with jerks from the very beginning of the disease.*"[6] These statements by Rose have been repeatedly verified by later observers.

Rose was a keen and careful observer, as may be seen from his description of his own cases and his critical remarks on the observations of his predecessors and contemporaries, but in other respects his judgment was less admirable, as when he believed that there was such a variety as "spontaneous tetanus" (the atypical tetanus of others of that day) that may appear quite suddenly without a previous injury. This type of the disease was, in his day, still thought to be quite different from traumatic tetanus in respect to its causes, among which were included exposure to cold, sudden suppression of perspiration, residence near the seashore, or even on the mountains, of tropical lands, and other mysterious influences. Even the judicious Curling, as we have seen, still admitted this form of tetanus, which,

[6] Italics ours.

as he says, occurs rarely in England and then only in a mild form. Many of Rose's contemporaries, however, both on the continent and in England, even at this time, refused to admit that there is any other variety of tetanus than the traumatic. It must also surprise the reader of this surgeon's treatise with its wealth of clinical material to learn that he refused to believe that local tetanus, in the sense in which this term is now and was already used in his day, ever occurs in human beings. Axhausen says that Rose thought that the belief in the occurrence of this type of tetanus was due to faulty observation. For Rose, as for the great majority of the surgeons of his and an earlier day, every form of tetanus begins with rigidity of the jaw muscles—an initial symptom that was always thought to occur no matter where the site of infection might be located. Rose pointed out that on palpating the anterior border of the masseter muscles by placing a finger in the mouth, one can recognize this rigidity in its earliest stages. In spite of the many sound critical remarks dispersed through his treatises, whose true significance was, however, entirely misinterpreted by him, Rose finally concluded that the disease is one involving the central nervous system only. The possibility of a peripheral action of the tetanus toxin on the voluntary muscles of the body was brushed aside as a secondary phenomenon whose true nature could be unmasked ("sich entlarven lassen") by a skilful deductive analysis.

The learned Brunner (13), to whom every student of tetanus must feel indebted, if only for his historical studies in relation to so many aspects of the disease, in speaking of the clinical observation that led Rose and his predecessors to make the statements cited above, pointed out that other surgeons, as Heine and Dupuytren, were led by their own observations to make the contrary assertion that the initial symptom in tetanus is dysphagia rather than trismus. Heine is quoted as saying, in his description of gunshot wounds of the extremities, that "almost all cases began with difficulty in swallowing which was followed after one or two days by trismus;" and Dupuytren is quoted as saying, in his "Traité des Blessures," "It is ordinarily the muscles of the pharynx that are first affected." In the years since these words were written numerous statements have appeared in the literature fully corroborating the observations of these two writers.

Tetanus is a disease of such varied symptoms, quite unpredictable in respect to the relative order of their appearance, that it is never safe to make positive assertions as to the rarity of this or that symptom or the relative order in which the symptoms occur.

Permin, who was also an upholder of the purely central theory of tetanus, makes the following remarks in relation to the points now under discussion: "It is certainly difficult to bring the conception that all cramps are of reflex nature into harmony with clinical and experimental observations. To him who has had the opportunity of studying a series of patients with tetanus the fact will have become quite clear that not all attacks of cramps (*Krampfanfälle*) can be of reflex character. While one may make the observation on one patient that a light blow, a mere touch, or a very mild sensation can cause a suddenly appearing state of contracture, one observes in other cases that repeated and rough manipulations, painful serum injections under the skin or into the spinal canal, and the like, leave the patient as undisturbed as if he had not been touched, even during a period of time in which it may be assumed that the spinal cord has had a long period of rest."

Klemm (29), writing in 1889, on the inadmissibility of retaining the designation "tetanus *hydrophobicus*" as an unusual form of tetanus *traumaticus*, made the following remarks concerning cases that are now classed as instances of head or cephalic tetanus: "As to their prognosis, therefore, cases in which the incubation period is of long duration and the reflex excitability of which is only slightly increased and in which *the generalized tetanic phenomena appear only very slowly or not at all*,[7] have a better chance of recovery than those in which this is not the case." Here also we have a student of tetanus who asserts that there are instances of the disease in which the generalized symptoms referable to reflex excitability may be entirely absent.

Brunner, who, of all writers, has made the most careful clinical observations on head tetanus since the days of Rose, and whose papers are most valuable particularly for his historical studies in reference to this variety of tetanus, as also for his experimental studies, in which every feature of this form of tetanus was reproduced in animals by injections either of the filtered toxin or virulent cultures, states

[7] Italics ours.

definitely that in the lighter forms of infection, in which the poison reaches muscles from the primary seat of infection, these locally poisoned muscles may be entirely free from centrally induced or "tonic cramps," and refers to this peripheral poisoning of the muscles as a "localized stationary tetanus."

Vaillard and Vincent (1891), who have made such fine contributions to our subject, must also be named with those who were not quite satisfied with the purely central explanation of the disease. They had the perspicacity to surmise that local tetanus might be due to a direct action of tetanus toxin on the muscles themselves, as may be seen from the following passage from one of their papers: "Mais il est d'autres faits que l'action exclusive du poison sur la moelle ne suffirait peut-être pas à expliquer. Tel est le début constant de la maladie par les muscles intéressés dans l'inoculation ou les plus voisins du point infecté; l'extension hémilatérale des symptômes du côté inoculé, et parfois leur limitation exacte à une moitié du corps. Telle est surtout la localisation absolue du tétanos à un groupe de muscles, lorsque la dose de toxine injectée dans un membre est extrêmement faible; *on peut même déterminer la contracture isolée et durable d'un seul muscle. La toxine se comporte alors comme un poison musculaire.*"[8] As far as we can learn, however, neither Vaillard nor any of his pupils give any experimental evidence in proof of the sound conjecture that the toxin behaves as if it were a muscle poison. But Vaillard's French contemporaries, Courmont and Doyon, very definitely opposed this view. They stated their opinion categorically in the following words: "Il n'en était rien, comme on la verra" and added, "En somme: *la toxine tétanique n'est pas un poison musculaire; elle agit sur la système nerveux.*"

Another French writer, Albert (1918), says: "It seems that there has been a tendency, as a general rule, to exaggerate the importance of the nerve pathway for tetanus. The absorption by peripheral nerves appears to me, on the contrary, to be a matter of entirely secondary importance, incapable of giving rise to a generalized tetanus and solely responsible for the atypical localized forms of the disease. Very severe tetanus of a generalized form is the result of absorption of the toxin par voie sanguine."

[8] Italics ours.

The surgeon Billroth (8) pointed out that "the fact that tetanus can be confined to a single extremity, even to one hand, speaks very much for a local action that involves only the nerves of the tetanized extremities," and in a later paper he remarks that individuals thus affected may recover without any other signs of the disease, a statement that has often been made both before and since.

As we approach the years of the last century that immediately precede and follow the period when the bacillary cause of tetanus was established, we come upon a host of writers who discovered instances of local tetanus that appeared in various parts of the body as the first symptom of the disease before any signs of descending tetanus were discernible. These writers were induced to describe their cases, because, in every instance, the observed local contractures appeared *first* in the immediate vicinity of the seat of infection, and because their persistence there, for a longer or shorter period of time after all other symptoms of the disease had disappeared, could not be brought into line with the classical theory of descending tetanus. Some of these writers, as Stintzing, Klemm, Esau, Goldscheider, Brunner, and a very considerable number of French and other writers that are cited by Courtois-Suffit and Giroux in their treatise on "The Abnormal Forms of Tetanus," have given us fine descriptions of local tetanus in various parts of the body, in every one of which the local contractures had their origin in the immediate neighborhood of the infected wound. It is repeatedly pointed out by many writers of this period, as Pochhammer and Klemm, that this very important earliest symptom of the disease has probably been overlooked in the great majority of instances.

We may here remark that writers on the tetanus of domestic animals have also very generally neglected to note and study this early manifestation of the disease; but the following statement is nevertheless found in a German treatise (27) on the disease of these animals: "Tetanus *partialis* is limited to the muscle cramp in individual parts of the body, and indeed, as a rule, to those that contain the site of the infection. Such partial forms of tetanus, if they remain permanently localized, are generally accompanied by mild symptoms and in their case the contracture of the poisoned muscle groups does not attain as high a degree as is the case in generalized tetanus. For the

most part, however, such forms of partial tetanus constitute only the beginning stage of the generalized form. In a case that was observed by Huygens in an animal with an injury of the neck there persisted lateral curvature of the neck on the injured side for twelve hours, whereupon this condition was rapidly followed by generalized convulsions." The writers of the treatise also refer to a long continuing rigidity of muscles that lasts from four to six weeks and finally disappears entirely, and very properly name it post-tetanic muscle rigidity. We may add that many instances of this muscle rigidity that persists for many months, and even for two or more years, are found in case histories of human tetanus.

We cannot here consider in detail such interesting cases of local tetanus as those described by Klemm (30), one of which involved the abdominal, thoracic and lumbar muscles of one side to such an extent that the trunk was curved rigidly to one side, thus affording an example of pleurothotonos; or that of Stintzing, in which all of the muscles of the entire right leg were thrown into local tetanus in consequence of a deeply lying infected area on the inner aspect of the upper thigh; or any of the many other examples of local, or so-called abnormal, forms of tetanus, that are to be found in the literature of the last quarter of the last century and from then on down to our time.[9] It is of interest, however, to learn how some of these writers analyzed and interpreted their observations. Klemm, for example, writes: "I am of the opinion that the observation of the patient whose symptoms have been described by me forces us to hold fast [*festhalten*] to a peripheral action of the tetanus poison." After further elaboration of his ideas on this point, Klemm concludes as follows: "If the toxin were to influence the central organ only, it would not be easy to explain just why the muscles that lie in the neighborhood of the seat of infection should be more strongly affected than others (as so clearly appears from my description of the symptoms of my patient) on the supposition that the poison is distributed uniformly throughout the entire central nervous system; if, however, we permit the assumption that an alteration occurs in the peripheral motor nerves in the sense

[9] The Treatise of Courtois-Suffit and Giroux, entitled "Les Formes Anormales du Tétanos," Paris, 1916, while not exhaustive, gives many instances of these local or abnormal types.

of my explanation given above, we would then have a thoroughly plausible explanation for the appearance of local tetanus which would be in entire conformity with our experience with tetanic patients." This author's explanation of the action of the toxin in causing local tetanus differs materially from that of Autokratow (2) and of Courmont and Doyon (15), who held that the toxin affects primarily the sensory nerve terminals of the muscles. Klemm was inclined to believe that "the motor nerves in the neighborhood of the site of infection are affected by the toxin in such a manner as to cause a molecular alteration of their structure, in consequence of which their resistance to the passage through them of motor impulses is so far lowered that these efferent impulses now cause a pathological type of muscle action that manifests itself in the form of a contracture [*Krampf*]."

Brunner, whose work was referred to above, finally also came to what he and other writers of his day called a double action of tetanus toxin. He expresses himself as follows: "We may picture to ourselves a double action of the toxin, that is to say, a combination of a local peripheral and a central action. We may assume that the local action of the toxin is not one that leads directly to contraction; it is only a prerequisite for the appearance and manifestation of its central action. As the poison spreads from the site of infection in the peripheral lymphatic networks it causes first an alteration in the peripheral organs, that is to say, in the muscles and nerves, which alteration now makes the corresponding neural centers susceptible to the toxin that has been carried to them in the blood stream. The centrally arising convulsions, that are made possible by the action of the poison on the centers, are manifested first in those peripheral nerve regions which were first affected by the poison." Brunner further states that "the toxin that is carried in the blood stream to the spinal cord and to the peripheral nerves belonging to them does, indeed, cause a state of increased reflex excitability, but cannot lead to permanent contracture;" and again, "the greater the amount of poison produced at the site of infection the more pronounced and the more widespread is the local action of the poison, but larger also is the amount of the poison that is carried in the blood to the centers and the periphery." It is clearly evident from the above citations from the writings of Brunner that he saw very clearly that the toxin of

tetanus displays "a combination of a local peripheral and a central action." He failed, however,to recognize the true nature of its local action, inasmuch as he concluded that "this local action does not directly lead to muscle contracture but is only a prerequisite for the appearance and maintenance of its central action." Goldscheider, writing in 1894, expressed much the same idea when he believed, as was pointed out in Paper II of our series, that the primary local tetanus and the later more generalized tetanic convulsions are both to be explained by a central action of the toxin, in that the toxin could so alter the state of excitability of axon terminals that their corresponding neurons in the cord would, in some unexplained manner, be themselves rendered more excitable by this action of the toxin on their peripheral terminations in the muscles. The assumption of Brunner and Goldscheider that the excitability of axon terminals may be a prerequisite to the central action of the toxin fell into disrepute when Meyer and Marie offered their sharply defined theory of the transfer of the toxin from motor axon terminals, via axis cylinders, to central motor nuclei, as a more rational solution of the affair.

After Brunner and his contemporaries, Zupnik, a young Privatdocent in internal medicine at Prague, is the next writer to offer experimental evidence in favor of the opinion expressed by Vaillard and Vincent, Heiberg and others named above, that the toxin acts directly upon all voluntary muscles with which it comes in contact. It has already been stated in Paper I of our series that this investigator was the first to show that even in the small animals used in laboratory experiments, local tetanus may be entirely avoided, if the toxin be injected into the subcutaneous tissues of the tip of the toes, the end of the tail, the dorsum of the foot, or into the neighborhood of certain joints that are not in contact with the body of a muscle. When due precautions are observed in experiments of this type, local tetanus, in the long accepted sense of the term, does not occur. For example, in place of a stiffened leg to start with, we now have a descending tetanus, the serial order of whose symptoms varies considerably in different species of animals.

Zupnik next tried to prove that local, or partial, tetanus wherever found is due to the direct action of the toxin on the voluntary muscles with which it comes in contact and is quite independent of any central

action. In order to furnish the desired proof for this assumption he transected, as he supposed, all of the nerves of the hind leg of a rabbit and then injected the toxin into the denervated leg. He claimed that now the muscles of the denervated leg were thrown into rigid contracture, exactly as is the case when the injections are made into the leg of an animal that has not been subjected to this operation. It was soon shown, however, by the surgeons Permin and Pochhammer, by the pharmacologists Fröhlich and Meyer and by Sawamura, that Zupnik's experiments could not be successfully repeated. It was definitely proved by these investigators that his experiments were faulty and that the deductions that were drawn from them were entirely without foundation. They were able to show that he had failed to denervate completely the muscles of the extremity into which he subsequently injected the toxin. It calls for very careful work on the part of the surgeon to denervate completely the hind extremity of a dog or rabbit so that not even a single small branch of the sciatic, the obturator, or the femoral nerve remains intact. We are entirely in agreement with Zupnik's critics. Prof. W. M. Firor and Dr. August F. Jonas, Jr., of the Department of Surgery of this University, have many times performed the operation for us, and it was always observed that if but a single branch of one of these nerves that innervate a leg remains uncut, the muscles controlled by this nerve will respond to the injected toxin in the usual manner by assuming a state of rigid contracture. Singularly enough, it appeared to us that in such instances of incomplete denervation, some apparently denervated muscles adjoining the non-denervated ones also assumed the rigid state. This observation, should it later be found to be true, would obviously be one of significance. If the denervation has been properly performed, so that it is really complete, the injection of an amount of toxin that ordinarily gives a perfectly rigid extremity, is entirely devoid of effect. It is certain then that Zupnik failed entirely to prove his contention that tetanus toxin acts in a direct and specific manner on voluntary muscles, irrespective of its central action. Zupnik also attempted to disprove the apparently well founded theory that tetanus toxin is conveyed to the central nervous system by way of motor nerves. In our Paper III we gave an account of his "crucial experiment," in the course of which he injected the toxin into the

posterior tibial nerve of a dog. Inasmuch as the injection was followed by descending tetanus, without any signs of a prior localized stiffness, he believed that the outcome of the experiment disproved the nerve transport theory.

In the course of our criticism of this crucial experiment of Zupnik in Paper III, we made the statement that "his contemporaries paid no attention whatever to this experiment." The statement was incorrect and was due entirely to an oversight on our part, as we found later that we had actually made full notes two years before on a critical analysis of Zupnik's experiment made by Fröhlich and Meyer as well as a description of their counter-experiment. They assert that Zupnik was bound *not* to induce local tetanus by injecting the toxin into the posterior tibial nerve, since this nerve "is almost exclusively of the sensory type [*Hautnerv*] and does not lead to the spinal motor cells of the leg muscles." They conclude that the injected toxin escaped from the ligated and greatly distended nerve, and not finding motor nerves close at hand by which it could ascend to the spinal cord (in accordance with their nerve transport theory), it could only make its way into the blood stream, from which it was taken up by the motor nerves of the head, neck and trunk, with the usual effect of causing a descending tetanus. But this interpretation of Zupnik's experiment is based on the now untenable theory of the centripetal carriage of the toxin to central nuclei, via motor nerves, and has therefore now lost its former significance. More space need not be given here to an analysis of the counter-experiment made by Fröhlich and Meyer, in which about one-third of a minimal lethal dose of toxin was injected into the posterior tibial nerve of the dog without calling forth either local or general tetanus—a fact that apparently fitted in well with the theory that purely sensory nerves, "while capable of conveying the toxin (37) more slowly than motor nerves, are nevertheless incapable of carrying it to motor centers." It is not surprising that one-third of a minimal lethal dose of toxin, when injected into the nerve in question at the point utilized by Zupnik, calls forth no symptoms of any kind. A study of our previous papers will make it quite evident that an intraneural injection of toxin when made into a posterior tibial nerve, at a point where the nerve is not surrounded by muscles that can be reached by toxin that leaks away from the injected nerve, is the equivalent of an intravenous injection of the same amount of toxin. Now the quantity of toxin employed by Fröhlich and Meyer without inducing tetanic symptoms of any kind can be injected into a dog (the animal used in their experiment), intravenously, intraperitoneally, into the testicle or into any properly selected muscle-free space, without inducing any symptoms whatever. Zupnik employed larger quantities of toxin in his "crucial experiment" and it was only natural that the symptoms of descending, blood-borne tetanus should appear. Had Fröhlich and Meyer injected a quantity of toxin into the posterior tibial nerve equal to that employed by Zupnik, they would not have been able to evade the consequences of blood-borne, descending tetanus. Their counter-experiment,

as described above, is entirely devoid of evidential value for their theory, now that it has been shown that peripheral nerve trunks do not constitute a pathway by which the toxin is carried to reacting cells of the central nervous system.

We may conclude our remarks on Zupnik's crucial experiment and Fröhlich and Meyer's criticism and counter-experiment by saying that neither of the contesting parties really proved his case. Zupnik's contention, however, that toxin is not conveyed to the central nervous system by peripheral nerves was really sound at bottom, despite his faulty technique, as was proved by us in Paper III of our series.

Zupnik next attempted to prove that "the second cardinal symptom of tetanus—the generalized reflexly-induced seizures—can be made to appear in pure form, unaccompanied by a permanent rigidity of muscles." By way of proof, a relatively large quantity of toxin, that varied from $\frac{1}{10}$ to $\frac{1}{2}$ of a minimal lethal dose, was injected into the spinal cord of cats. After an incubation period of only fourteen hours it was observed that heightened reflex excitability appeared in one of the legs innervated by the injected part of the cord. Soon thereafter the fellow leg responded to reflex stimulation, and, in further course, the other extremities, and finally the entire musculature of the body became hyperresponsive to sensory stimuli. The reflex activity of the central nervous system was now so greatly exaggerated that lightly touching the animal or even blowing at it with the breath caused generalized extensor convulsions of all extremities, and even opisthotonos. Zupnik emphasizes the fact that the *reflexly contracted muscles immediately relaxed and became soft as soon as the reflex convulsions subsided.*[10] In a word, in this form of experiment in which the toxin was injected directly into the spinal cord, only periods of reflexly-induced convulsions were observed, without any evidence of continuously rigid contractures of voluntary muscles. Unfortunately, Zupnik fails to give us any data in regard to the part of the spinal cord into which the injections were made, or to the volume of the injected solution or to the subsequent fate of his animals. But his claim that intraspinally injected toxin does not evoke sustained contractures of any voluntary muscles, but only a hyperexcitable state of central nuclei, did not long remain unchallenged. Fröhlich and Meyer and Loewi and Meyer thought they could demonstrate that the direct injection of large quantities of the toxin into the lumbar spinal

[10] Italics ours.

cord of toads, frogs, rabbits and cats, does induce, after a short period of incubation, not only a truly and permanently rigid state of voluntary muscles but, also, very pronounced reflex seizures. The experiments of these authors, together with those of Liljestrand and Magnus, Keller and others, appeared to be so irrefutable that the theory of a two-fold action of tetanus toxin was thought to be completely discredited. We shall have occasion later (Paper VI) to inquire into the validity and true significance of the experiments of these authors, more particularly that of their cord injections, which are stated to have been followed by sustained contractures of leg muscles.

The theory that the *natural* disease, tetanus, may be characterized by *two* distinctly separate but generally associated types of "cardinal symptoms," in consequence of this double action of its toxin, is no longer mentioned in the textbooks of neurology, medicine, surgery or bacteriology of our day, except occasionally as a historical note, in one of the larger handbooks on bacterial diseases (20), and then only to serve as an instance of an earlier and discarded hypothesis that lacked experimental verification. Our critical analysis of the literature bearing on the points at issue discloses the reasons why the dissenters from the prevailing central theory were unable to justify their opposition to it. The experimental evidence offered by them in support of their position could not always be verified, and, too often, it involved vague and unproved assumptions that were as unacceptable to their contemporaries as they are to us.

It will be apparent to the readers of our preceding papers and of these historical notes that the history of tetanus is one of conflicting opinions, not only in respect to the true explanation of the many facts that have been brought to light by the intensive laboratory investigation of the past fifty years, but equally so in respect to the pathogeny of the multiform symptoms of the disease. In papers that will follow the above historical notes and commentaries, we shall offer many experiments in support of a point of view that is capable of reconciling the facts disclosed by experiment, with those observed at the bedside.

A theory of the nature of tetanus, as was remarked in the introduction of the present paper, that fails to satisfy, clearly and easily, the requirements of such a reconciliation, cannot hope to survive. Two of the facts that have already been established by us, (1) that tetanus

toxin is not conveyed to the central nervous system via peripheral nerves, and (2) that it acts very directly and in a specific manner on voluntary muscles with intact neural terminals, irrespective of the pathway by which it reaches them, can both easily be brought into agreement with some of the most important symptoms of human tetanus without violating any accepted tenet of muscle or nerve physiology. As far as we can judge at the moment, our point of view, which will be more fully elaborated after the completion of our work on the results of intraspinal injections of the toxin, accounts in an equally satisfactory manner for all of the other symptoms of the disease.

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(56) *Idem:* Die Pathogenese des Tetanus. *Ibid.*, 1905, xxxi, 1999–2004.

(57) *Idem:* Bemerkungen zu Pochhammers Aufsatz: "Der lokale Tetanus und seine Entstehung." *Ibid.*, 1908, xxxiv, 1144.

COMPENSATORY CHANGES IN THE REMAINING LUNG FOLLOWING TOTAL PNEUMONECTOMY

An Experimental Study

WILLIAM F. RIENHOFF, Jr., FRED L. REICHERT and GEORGE J. HEUER

Introduction. Early in 1914 a group of workers including Heuer, Andrus, Cave, Dunn, E. Holman, Rienhoff and Reichert, began a series of experimental observations bearing upon lobectomy and pneumonectomy in the dog. Their purpose was to develop safe methods for closing the bronchial stump, to observe the effect of ablation of one lung upon the pulse, blood pressure and respiration, to determine the fate of the empty pleural cavity left after the ablation, and to discover the anatomical and the physiological compensatory mechanisms by means of which the animal could carry on after total removal of one lung. A series of papers by Heuer and Dunn,[1] Heuer and Andrus,[2] and Andrus[3] were published between 1920 and 1923 dealing with these various aspects of the subject; but one interesting phase of the work was at that time left unstudied. It was found that when one lung was removed, the remaining one enlarged to a surprising degree and within a comparatively short time came to occupy the entire thoracic cavity except the space retained by the heart and mediastinal structures. This was held to be a compensatory enlargement and was shown later to bear a relationship to the physiological compensatory mechanisms that occur, but its exact nature was not determined. The present study has been undertaken to determine whether this enlargement is due to (1) hypertrophy, (2) hyperplasia, (3) emphysema or (4) simple dilatation of the pre-existing respiratory unit.

Materials and methods. The material for this study was obtained

[1] Heuer, George J., and Dunn, George R.: *Bull. Johns Hopkins Hosp.*, **31**, 348, 1920.

[2] Heuer, George J., and Andrus, W.: *Ibid.*, **33**, 130, 1922.

[3] Heuer, George J., and Andrus, W.: *Ibid.*, **34**, 119, 1923.

from a series of 10 dogs which had been subjected to a total left pneumonectomy. The specimen of lung removed under the most careful operative technique, and distended to a degree representing the normal within the thorax, was studied not only by the injection and corrosion method but also by the wax plate reconstruction of Born, thereby enabling us to observe changes in the bronchial tree as well as in the terminal respiratory unit. Histological studies were made also to determine the size of the terminal alveoli, the relative thickness of their walls, the status of the surrounding capillary bed, and the presence of elastic tissue.

The accurate determination of the amount of intrapulmonic pressure required to distend the lung to its normal volume in the living animal was of primary importance, and had to be arrived at before it would be possible to compare anatomically the lung removed at operation with the remaining lung which subsequently increased in size. The technique used in this determination was as follows: By resection of ribs, windows were made in the chest wall, which permitted direct observation. With an occluding ligature placed cephalad to the point of insertion of a needle into the trachea, the exact pressure (as measured by a mercury manometer) necessary to distend the lungs so that they completely fill the thoracic cavity could be determined by forcing air slowly into the bronchial tree. At different atmospheric pressures and periods of time after death it was repeatedly noted that the expanding lung came up to and was flush with the anterior and lateral thoracic walls when the manometer registered a positive pressure of 10 mm. of mercury. With a pressure of 12 to 15 mm., the lung bulges through the thoracic windows but the ribs remain in their fixed position. The thoracic cage begins to enlarge and the ribs are made to change their position caused by the pressure of the confined and distended lung, by increasing the intrapulmonic pressure to 30 mm. Opening the abdomen had absolutely no effect upon the pressure readings in this series. In another series of animals sacrificed for other reasons, in which observations were made immediately after death, a different method of distension was used in order to obtain the optimal pressure, and the results were found to agree with those of the previous series. In these animals the trachea was clamped off, and a needle was thrust into the thoracic cavity which then gave a reading of −4 to

−5 mm. of mercury. These same figures were also obtained with the needle in the trachea, and whether the needle was in the trachea or in the right or left thoracic cavity, the pressure was found invariably to be between −4 and −5 mm. On opening the abdomen in order to observe any movement in the diaphragm, it was found that, simultaneously with movement of the diaphragm, expansion of the ribs began, whereupon the reading on the manometer would rise to +14 or +15 mm. The inflation of the lungs was repeated several times in each animal and the air was then allowed to escape from the trachea, with the result that the pressure again fell to −4 to −5 mm. On re-introduction of the air to cause expansion of the ribs and diaphragm, the pressure would again reach +14 and +15. In this state of distension, when an opening was made in the diaphragm while the pressure was +14 and +15 mm., the mercury dropped to between 9 and 10. At this latter pressure the lungs were found to be moderately distended so that they were just touching the lateral, anterior and posterior walls. In animals which had been dead for a number of hours it was noted that certain areas in the lung were atelectatic, and to overcome this condition it was found necessary to raise the intrapulmonic pressure gradually to 30 mm. or slightly over, so that every portion of the lung tissue became fully distended. The atelectatic areas disappeared and when the pressure was raised to 10 mm., no blebs could be seen under the visceral pleura and all the lobes were moderately and evenly distended at the optimal pressure. In order to be certain of the uniform inflation of the lung, all specimens were at first fully distended to 30 mm., and the pressure was then lowered to the optimal point and the lung fixed. The volume of the lung was also measured by placing carefully removed and intact specimens in large graduated cylinders and determining the volume of water displaced. The inflation of the lung, *in situ* or after removal, gave the same volumetric readings as the distension with fixation or with simple distension with air.

Another small series of 4 animals were observed while under ether just before being sacrificed and, as was expected, depending on the degree of anesthesia, the respirations were found to vary in depth. The variations in pressure changes with shallow respirations compared with those associated with deep breathing were noted, and it was

found that the lungs were completely distended and in contact with the chest wall when the pressure reached a little above 10 mm. of mercury. On the basis of these data it seemed best to study the operative and autopsy specimens when distended with a final pressure of 10 mm. of mercury, while at this same degree of inflation it seemed advantageous to compare the lobes of the lung removed at operation with those left for longer periods of observation. Fixation of the lung was accomplished by Miller's method, as illustrated by Gardner,[4] and was found to be very satisfactory. The operation and, later, the autopsy specimens were treated in exactly the same way. Great care was exercised in the removal of the specimens, so that no injury, such as tearing of the visceral pleura, occurred. The lobes were injected and distended while immersed in a dish of warm salt solution. In the operation specimens a needle was inserted into the left primary bronchus or one of its branches and in the autopsy specimen into the trachea, and the intrapulmonary pressure was slowly raised until all the atelectatic areas were obliterated, but the pressure was never allowed to exceed 35 mm. of mercury. It was then gradually lowered until it remained stationary at 10 mm. At this stage, 10 to 15 cm. of Zencker's solution were gradually run in through the needle, the pressure being kept at exactly 10 mm. of mercury. After distension of the lobes, the blood vessels were washed out with warm saline, the arteries being then injected with carmine gelatin, and the veins with Prussian blue. The specimen was put into a jar containing Zencker's solution which was then inverted. After fixation, blocks for section were carefully cut with a Gillette razor blade and the tissue prepared in celloidin. In order to determine whether or not there was an increase in number of branchings of the bronchial tree, which one would expect in the event of a hyperplasia, or whether or not there was an increase in its size, which might be associated with a hyperplasia or hypertrophy, from several celloidin preparations counts were made of the number of branchings of the bronchial tree to the terminal air sacs. The lobes were inflated to 10 mm. of pressure as usual, the blood vessels washed out with warm saline followed by a small amount of acetone, and then a mercurous sulphide (red) celloidin mass was injected into

[4] Gardner, Leroy M.: Studies on the Relation of Mineral Dust to Tuberculosis. *Amer. Review of Tuberculosis*, 1920, 4, p. 741.

the arteries, and one of Prussian blue into the veins. Giving time for these masses to begin to harden, air was slowly released from the bronchi, and chrome yellow celloidin was injected until the terminal air sacs were seen to be filling. The tissue was then digested away with hydrochloric acid and pepsin, leaving the visceral and bronchial systems accessible for study. On making counts of a normal mediastinal lobe and of one removed nearly six months after a left pneumonectomy, it was found that the branches of the bronchi in similar positions in five different regions of these two specimens showed the same number of branchings to the terminal air sacs:

Normal	*Distended*
7	7
7	7
6	6
7	7
7	7

A comparison of the number of divisions of the arteries and veins as well as their size, although not expected to be accurate, because there was no terminal unit, showed a close similarity.

Normal		*Distended*	
Arteries	Veins	Arteries	Veins
7	6	6	7
6	7	7	7
8	7	8	6
7	6	8	7

It was realized, however, that in order to come to any definite conclusion in regard to the increase of the actual alveoli and of the terminal respiratory lobules, a histological study, involving an actual count of the number of alveoli in a given microscopic field, together with a wax reconstruction of equal-sized blocks of tissue from similar locations removed from the operative and autopsy specimens, would be necessary. This study was carried out on one of the dogs of the series (F-6). This animal was subjected to a total left pneumonectomy on June 17, 1921. The left lung was excised, two ligatures being placed on the left primary bronchus. The specimen was treated according to the technique described above. After appropriate distension, the arteries were injected with carmine gelatin and the veins with Prussian blue.

The specimen was hardened in Zencker's solution at 10 mm. of mercury pressure. The dog was sacrificed on December 19, 1922. The trachea was clamped off and the lungs were distended *in situ* at 15 mm. pressure. X-rays were taken with the lung distended (No. 4882, 11 x 14). The remaining right lung was found to be very much enlarged, filling the entire thoracic space on the right side and extending into the left thoracic cavity through the anterior as well as the posterior mediastinum. The heart had been pushed over against the left thoracic wall. The lung was removed and the specimen treated according to the above described technique. Blocks were cut of exactly the same size and from corresponding locations as from the operation specimen removed in June. After fixation in celloidin, serial sections were cut, 1 to 25, each at 40 micra, and stained with hematoxylin-eosin for the wax reconstruction. Others, a smaller series, were cut at 10 and 20 micra for the histological study and for treatment with Weigert's stain for elastic tissue. The histological studies were made from the slides of 10 and 20 micra in thickness. The blocks of tissue from the operation and autopsy specimens were 2 mm. in breadth and length. Twenty-five sections were cut from each of these blocks at a thickness of 40 micra. These were thrown on the screen and photographed on bromide plates at a magnification of 50 times. They were then transferred from the bromide film to a 2 mm. wax plate by tracing with a steel stilette. Correct stacking and orientation of the slides and plates were made with relative ease due to prominent landmarks such as bronchi, blood vessels, and lines made through the bromide plates at the time of photographing. After the model was completed in wax and stacked, Potter's plaster was poured into the labyrinthian plexus of spaces representing the bronchial tree and respiratory units, which had been cut out after the tracings had been made from the wax plates. The paraffin block containing the plaster was then melted off in hot water just under boiling. After the model had been allowed to dry for several days it was impregnated with equal parts of paraffin and beeswax at 90°C. After being allowed to stand for a month, it was stained with oil colors, and drawings were made by Mr. James F. Didusch of the Carnegie Institute of Embryology. These drawings are reproduced in figures 1 and 2. It is to be noted that when figure 1, the operation specimen removed in June, is compared with figure 2,

the autopsy specimen removed in December—practically six months later—there is a very marked dilatation of the terminal respiratory

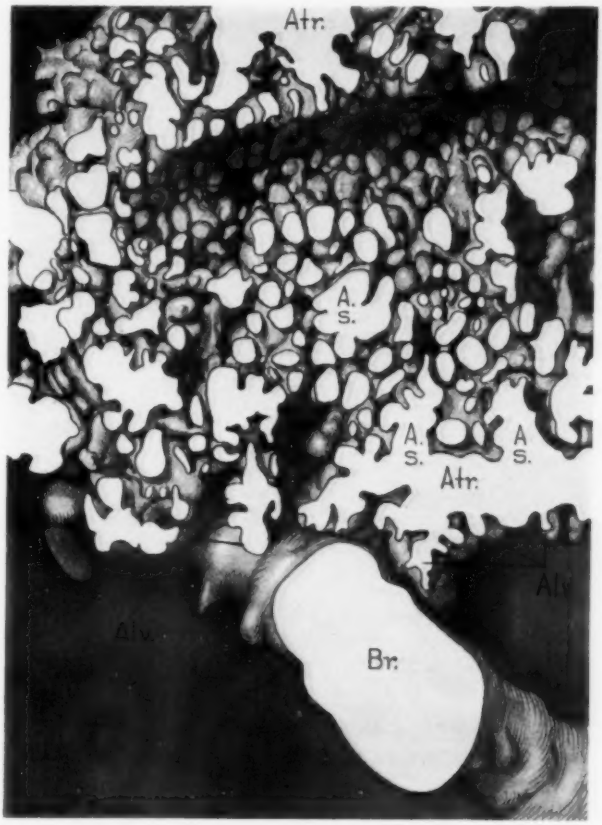

FIG. 1. WAX RECONSTRUCTION OF NORMAL LEFT LUNG OF DOG REMOVED AT OPERATION

br., bronchioli respiratorii; *atr.*, atria; *as.*, sacculi alveolares; and *alv.*, alveoli

unit, the alveolar ducts, the atria, the air sacs and the alveoli. No difference could be noted in the model in other parts of the bronchial or blood vascular system. The alveoli in figure 1 almost double in

number those in figure 2. The quite marked increase in size in the ductuli alveolares is not so apparent in the drawing as in a more

FIG. 2. WAX RECONSTRUCTION OF REMAINING RIGHT LUNG OF DOG SIX MONTHS FOLLOWING TOTAL PNEUMONECTOMY, LEFT SIDE

br., bronchioli respiratorii; *atr.*, atria; *as.*, sacculi alveolares; and *alv.*, alveoli

intimate study of the model, because they are situated more deeply and the drawings present merely the cut surface of the model.

In summary, it is believed that from the standpoint of the studies of

the corrosion preparations which showed no increase in the branchings of the bronchial tree, and of the models which showed a pronounced dilatation of the terminal portion of the respiratory unit or, in the terminology of Miller (5), the respiratory lobules,[5] the increase in the volume of the portion of the lung remaining is due mainly to a dilata-

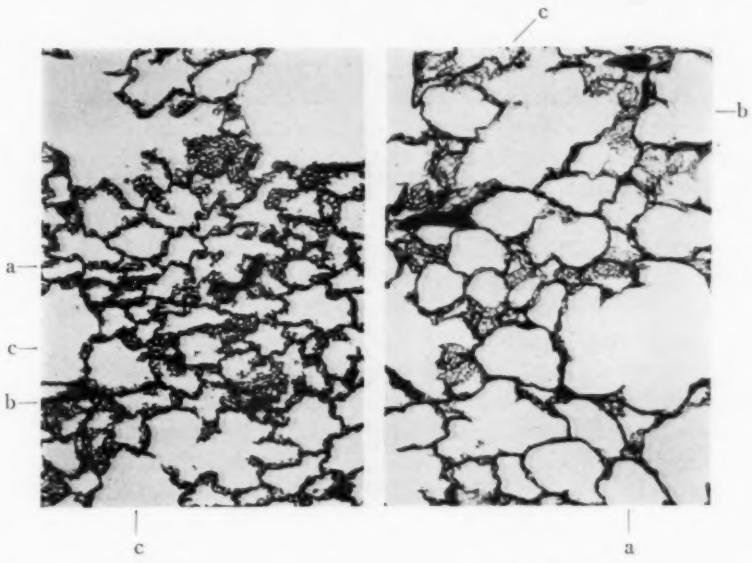

FIG. 3 FIG. 4

FIG. 3. MICROSCOPIC SECTION OF NORMAL DOG'S LUNG, CUT 10 MICRA IN THICKNESS, REMOVED AT OPERATION

a, alveolus; *b*, air sac; *c*, ductus alveolaris

FIG. 4. MICROSCOPIC SECTION OF DOG'S LUNG, 10 MICRA, REMOVED AT AUTOPSY SIX MONTHS FOLLOWING OPERATION

a, alveolus; *b*, air sac; *c*, ductus alveolaris

tion of pre-existing structures and not to a hyperplasia or an additional new growth of the parenchyma. To determine whether this dilatation is of the nature of emphysema, or rather of a true compensatory

[5] Miller, Wm. Snow: *Amer. Review of Tuberculosis*, Vol. 11, No. 1, March 1925. (The terminology used is that suggested by Dr. Miller).

physiological dilatation, it was necessary to resort to a study of the more detailed histological features of the respiratory unit that were revealed by the series of sections cut in 10 and 20 micra thicknesses. The microscopic sections (figs. 3 and 4) were even more confirmatory than the model in showing that the increase in the remaining lung was due to a pronounced dilatation of the ductus alveolaris, the atria, the sacculi alveolares, and the alveoli, or in other words, the respiratory unit. The interalveolar septa were thinner than normal and the capillary bed embracing the alveoli was not increased in amount but, on the contrary, the interstices in the capillary plexus seemed to be larger than those in the normal lung, thus denoting a diminution in the size of the capillaries. No difference could be made out between the normal and the abnormal specimen of the lung as regards the presence of elastic tissue. Perhaps it may have seemed slightly, but very slightly, more sparse in the autopsy than in the operation specimen, but there was no suggestion of absence or fragmentation of elastic tissue as seen in pathological or senile emphysema. There was no suggestion in the autopsy specimen of fusion of numerous alveoli so characteristic of emphysematous states. A further numerical confirmation of the observations above referred to was revealed in the comparative measurements of the size of 1000 alveoli counted in the normal lung and of another 1000 in a lung which had remained in the animal for six months longer. This count revealed the fact that in a 200 mm. square the number of alveoli in the normal lung averaged around 101 to 105 per 200 mm., while in the lung allowed to remain in the dog six months the average alveolar count was from 66 to 68 per 200 mm. square. The average dimension through the greatest diameter of the alveolus, found in a count, varied from 125 to 140 micra in the abnormal or autopsy specimen, and in the normal lung from 75 to 82 micra.

Conclusions. The compensatory changes in the remaining lung following total pneumonectomy in dogs consist of simple dilatation of the respiratory lobules or the definitive respiratory units made up of the bronchiolus respiratorius, the ductus alveolaris, the atria, the sacculi alveolares, and the alveoli. This dilatation comes in response to increased physiological demands and is of a compensatory nature. It is in no sense of the word an emphysema and there is no interruption or diminution of the elastic tissue or fusion of the alveoli to suggest

pathological change in the lung parenchyma. There is no increase in the number of the bronchial trees or in their pattern, and apparently the blood vascular system, except for a possible dilatation, is unaffected. No evidence of a true hyperplasia or an hypertrophy was found. The lack of uniformity of dilatation of the alveoli in any one section was found to be due to the fact that the serial sections cut through the alveoli at different levels of the block of tissue. The maximum diameter of different alveoli is, of course, situated in different planes.

EXPERIMENTAL GASTRECTOMY

Effects on the Blood Morphology, Especially When Complicated by Infection or Liver Damage[1]

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Pernicious anemia following total gastrectomy has been reported in human beings. Hartman (16), Dennig (6), Breitenbach (2), Poole and Foster (35), Ungley (43), and Treupel (42) each described one case. Hurst (18) cited three such cases. In addition, severe anemia, doubtfully Addisonian, was observed after gastrectomy in the cases of Moynihan (33) and of Cohn (4). Macrocytic anemia has not, however, invariably developed following complete extirpation of the stomach. In explanation of this, Poole and Foster suggested that perhaps all patients submitted to total resection of the stomach would develop pernicious anemia if they were to live long enough after the operation. In 1929, Finney and Rienhoff (8) were able to find reports of only 31 patients who had survived total gastrectomy, and in most instances the survival period was very brief. Only 10 patients had lived as long as one year. In the cases in which pernicious anemia developed, the time after operation at which the blood change was noted varied from 5 months in the case reported by Ungley to 8 years in the case reported by Dennig. Thus, the cases of pernicious anemia which have followed total stomach resections form a significant proportion of those in which the patients have survived the operation for a year or more.

Seventeen cases of macrocytic anemia which followed partial gastrectomy have been reported, and 13 cases followed gastro-enterostomy. Most of these were more or less typical of Addisonian anemia.

[1] Aided by a grant from the Ella Sachs Plotz Foundation.

[2] Stephen C. Clark Fellow in Surgery.

Two (5, 31) were described as showing aplastic anemia, although both patients had high color indices, and liver therapy, attempted in one of them, was successful. In two patients (7), each with a gastro-jejunocolic fistula, the blood was said to resemble that of sprue. In 3 instances (15) the anemia was slight but "megalocytic." References to these cases are included in the reports of Lublin (25), Hurst (19), Goldhamer (9), Larsen (24), and Hartman and Eusterman (17).

These cases of macrocytic anemia following partial gastrectomy and gastro-enterostomy, however, form only a very small proportion of the total number surviving these operative procedures, and it must be doubted whether the anemia was the consequence of the gastric defect. A much more common finding in patients who have undergone partial gastric operations is hypochromic microcytic anemia which resembles the so-called "idiopathic hypochromic anemia" (45). More than 270 such cases have been reported. The larger series of cases have been studied by Morley and Roberts (32), Gordon-Taylor *et al.* (12), Lublin (25), Larsen (24), Meulengracht (29), and Hartfall (15), and in these papers may be found references to the other reports.

In the lower animals total gastrectomy has not resulted in the production of macrocytic anemia. In gastrectomized rats hypochromic microcytic anemia has been observed (26, 22), and similar changes have been noted in monkeys (10) and in pigs (1, 27). In dogs, Mann and Graham (28), who made studies extending over several years, found that spontaneous anemia occurred rarely, but Gutzeit (13) reported that "aplastic hypochromic" anemia developed invariably, soon after gastrectomy. Ivy and others (20) observed spontaneous anemia only occasionally, but anemia regularly appeared in pregnant gastrectomized dogs. The spontaneous anemia was microcytic, although the anemia associated with pregnancy may have been, in one instance at least, macrocytic.

Failure to produce macrocytic anemia experimentally by means of total gastric resection might be interpreted to be a contradiction of Castle's hypothesis (3) that macrocytic anemia results from the lack of an antianemic principle formed by the interaction of a substance in the diet and an "intrinsic factor" secreted by the stomach. It has also been suggested that the dog, rat and pig are so constituted

biologically that they do not develop the blood picture of pernicious anemia (21, 28).

The latter argument seems unsound, however, for several reasons. "Intrinsic factor" has been demonstrated in the stomachs of dogs (14, 21), and pigs (21); antianemic principle is known to be present in the livers of these animals (41, 21); and the quantity of this principle in the liver of the pig decreases following total gastrectomy (1, 11). Furthermore, Seyderhelm and his associates (38) have reported macrocytic anemia in dogs, which they produced by causing partial obstruction of the lower ileum. Finally, fetal blood formation, to which the blood changes in pernicious anemia may be compared, is similar in the pig, dog, rat, rabbit and cat to that in man (48, 49).

It is generally recognized that the magnitude of hemopoietic response to liver therapy in cases of pernicious anemia is related to the quantity of liver administered. It is plausible that the converse is also true; namely, that the reduction in number of red corpuscles resulting from deficiency of antianemic principle depends on the degree of deficiency. It seems probable, therefore, that macrocytic anemia has not been successfully reproduced in animals by surgical means because the deficiency produced has not been sufficiently great. Meulengracht (30) has recently confirmed Sharpe's (39) observation that desiccated hog duodenum contains the antianemic principle. In order to produce macrocytic anemia experimentally in the pig, therefore, it would be also necessary to remove this source of antianemic factor, or to cause in some other way a deficiency greater than that which follows removal of the stomach alone.

For some time we have been interested in macrocytic anemia associated with disorders of the liver. We were led to suggest from our clinical observations (46, 44) that macrocytic anemia may occur not only because of absence of the intrinsic factor in the gastric juice, insufficiency of the extrinsic factor in the diet, or extensive disease of the liver, impairing storage of the hematopoietic principle, but also because of the combination of partial disturbance of alimentary secretion and moderate liver damage. It was the primary object of this investigation to test this hypothesis by observing the blood changes in gastrectomized dogs in which, in addition, liver damage had been produced.

EXPERIMENTAL OBSERVATIONS

Mongrel dogs were gastrectomized in a one-stage operation, with transplantation of the diaphragm on the esophagus about 2 cm. above the cardia, and esophago-duodenal end-to-end anastomosis. A number of the gastrectomies were performed by Dr. W. M. Firor to whom we are greatly indebted. Proof of completeness of operation was obtained by gross and microscopic examination of the anastomosis at autopsy.

Nineteen dogs were subjected to this operation while one was used to determine the influence, if any, of the diet on which the gastrectomized dogs were maintained. This diet consisted of cow's milk and canned ox-tail soup *ad libitum*, and cod liver oil occasionally. During a period of five months no anemia developed in the control dog, nor did symptoms of any kind appear other than loss of 1 kgm. in weight (original weight 8 kgm.).

In addition, subtotal gastric resection was performed in three dogs. In two (A 122 and A 125) the entire fundus and part of the pylorus and cardia were excised with end-to-end gastrogastrostomy. At postmortem examination, made a number of weeks later, it was found that one and one-half inches of the cardiac and of the pyloric portions of the stomach remained. In one dog (A 123) all of the pylorus and fundus and part of the cardiac end were resected, with end-to-side gastroduodenostomy. At autopsy about one inch of the cardiac portion was found but no other stomach tissue remained. The adjoining portion of the duodenum was found to be dilated.

Blood (3 cc.) was drawn from the jugular vein at frequent (usually weekly) intervals for complete blood studies. The methods used have been described elsewhere (47).

Distemper vaccine and virus were given to only a few of the dogs.

Effects of total gastrectomy.—Thirteen dogs died in 1 to 3 days following operation. The cause of death was shock, leakage of the anastomosis, distemper, or pneumonia. One dog died after 9 days of pneumonia.

In table 1 are summarized the changes in the blood of the dogs which survived the operation.

During the first month after total gastrectomy, 6 of 7 animals developed some degree of anemia; in 4 dogs with no postoperative complications, slight anemia, normocytic in character, was observed; in one animal (A 63) which had mild distemper, moderate anemia occurred; and in one with severe, fatal, distemper (A 68), marked anemia, simple microcytic in type, developed (fig. 3).

In the subtotally gastrectomized dogs, anemia failed to develop in periods of 3 to 13 weeks.

TABLE 1

Blood changes in gastrectomized dogs

NO. OF ANIMAL	TYPICAL BLOOD FINDINGS BEFORE AND AFTER OPERATION							ONSET OF ANEMIA, DAYS, P.O.	PERIOD OF OBSERVATION, WEEKS	COMPLICATIONS	SUBSEQUENT COURSE
	R.B.C.*	Hgb.	Ht.	C.V.	C.H.	C.C.	Days, P.O.				
Totally gastrectomized dogs											
A 63	7.07	15.1	47.8	68	21	31	0	10	8	Mild distemper 2 weeks P.O.	Died of acute CCl_4 poisoning
	5.20	11.0	35.5	68	21	31	37				
A 67	7.46	14.3	46.0	62	19	31	0	3	5	None	Died of acute CCl_4 poisoning
	5.52	9.9	34.5	62	18	29	31				
A 68	7.32	16.0	53.0	72	22	30	0	16	5	Severe distemper 3 weeks P.O.	Died of distemper
	6.26	12.7	40.0	64	20	32	16				
	3.54	5.7	19.0	54	16	30	30				
A 69	7.20	14.0	48.0	67	19	31	0	7	5	None	CCl_4 treatment begun 34 days after operation. See fig. 2
	5.54	11.6	41.0	68	21	29	7				
A 87	6.92	13.9	46.8	68	20	30	0	No anemia	4	None	CCl_4 treatment begun 26 days after operation. See fig. 4
	6.76	13.0	43.2	64	19	30	17				
A †	8.13	15.8					0	7	5	None	Refused diet 5 weeks P.O. and died within a few days
	5.19	12.1					18				
B †	7.20	14.0					0	7	5	None	Same as above
	5.45	11.9					26				
Subtotally gastrectomized dogs											
A 122	6.81	13.3	44.0	65	20	30	0	No anemia	6	None	
	6.36	13.9	41.1	65	22	34	24				
A 123	6.67	13.9	44.8	67	21	31	0	No anemia	13	None	CCl_4 treatment begun 86 days after operation. No anemia developed
	6.65	14.5	43.1	65	22	34	32				
	6.83	13.9	44.0	65	20	32	123				
A 125	6.81	13.3	43.0	63	20	31	0	No anemia	3	None	
	7.61	15.1	48.1	63	20	31	14				
Mean values for normal dogs. (See no. 47)											
Mean.....	7.02	14.6	47.3	67.6	21.2	31.4					
S.D.....	0.66	1.4	4.7	3.6	1.4	1.6					

* R.B.C. = erythrocytes, in millions per cmm.; Hgb. = hemoglobin, in gm. per 100 cc.; Ht. = volume of packed red cells, in cc. per 100 cc.; C.V. = mean corpuscular volume, in cubic microns; C.H. = mean corpuscular hemoglobin, in micromicrograms; C.C. = mean corpuscular hemoglobin concentration, in per cent; S.D. = standard deviation; P.O. = after operation.

† Included from a series previously studied by one of us (H. B. S., Jr.) in collaboration with L. B. Edwards and C. Bernstein, Jr. (Unpublished data.)

In two totally gastrectomized animals in which such studies were made (A 69, A 87), a constant reduction in the refractive index of the blood plasma was noted. The refractive index ranged between 1.3430 and 1.3450, whereas the normal values are 1.3484 to 1.3508. Calculated in terms of serum protein the values for the gastrectomized animals ranged from 3.0 to 4.0 grams per cent, those of normal dogs

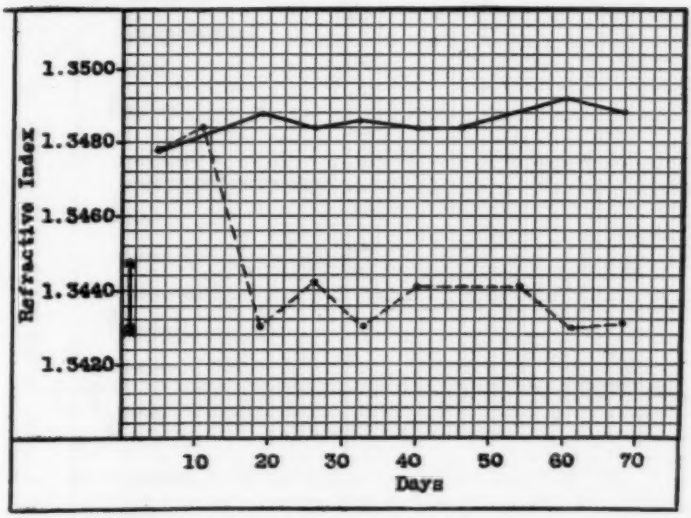

FIG. 1. THE REFRACTIVE INDEX OF THE BLOOD PLASMA OF A TOTALLY GASTRECTOMIZED DOG COMPARED WITH THAT OF A CONTROL ANIMAL TAKING THE SAME DIET.

Continuous line: control. *Interrupted line:* gastrectomized dog. The arrow indicates the day of operation.

from 5.7 to 6.9 grams per cent. In two subtotally gastrectomized dogs no decrease in the refractive index was found. The studies in one totally gastrectomized dog are compared in figure 1 with observations in a control animal.

Liver damage and gastrectomy.—Lamson and Wing (23), as well as others, have demonstrated that repeated doses of carbon tetrachloride, given to dogs by gavage, cause necrosis and, eventually, cirrhosis of

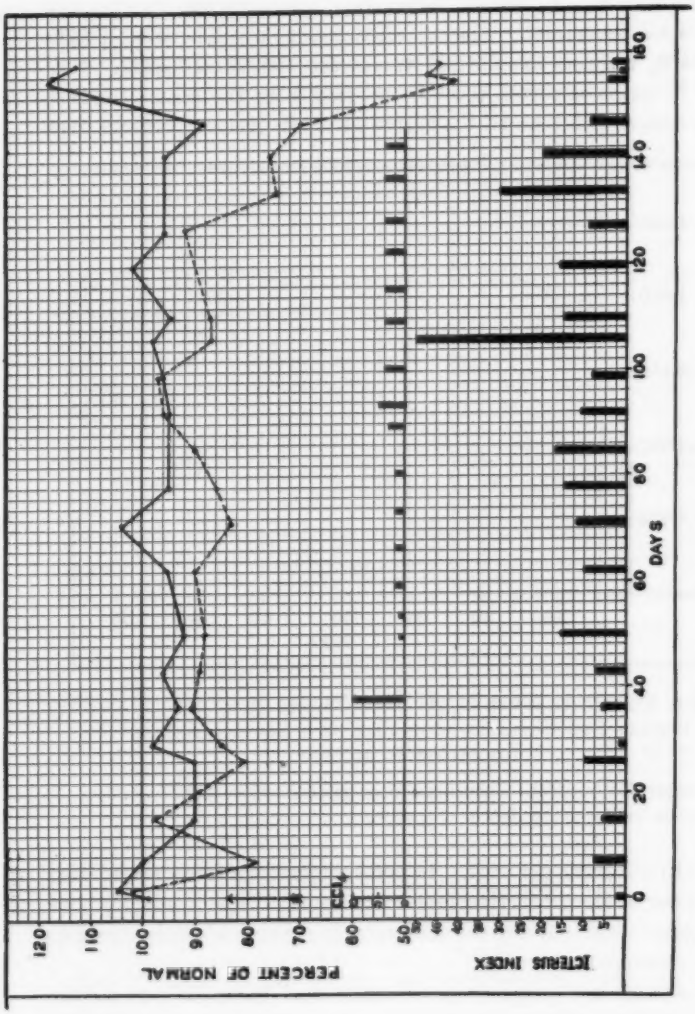

FIG. 2. CHANGES IN THE BLOOD OF DOG A 69

Arrow indicates day of gastrectomy.
Continuous line: mean corpuscular volume. *Interrupted line:* erythrocyte count.
All values are expressed in proportion to the normal.

the liver. We have used this drug to produce liver damage in normal dogs (40) and employed it with the same object in the gastrectomized dogs.

The totally gastrectomized dog is apparently extremely sensitive to carbon tetrachloride. Thirty-three, 35, and 52 days after operation three dogs were given initial doses of 10 cc. each by stomach tube

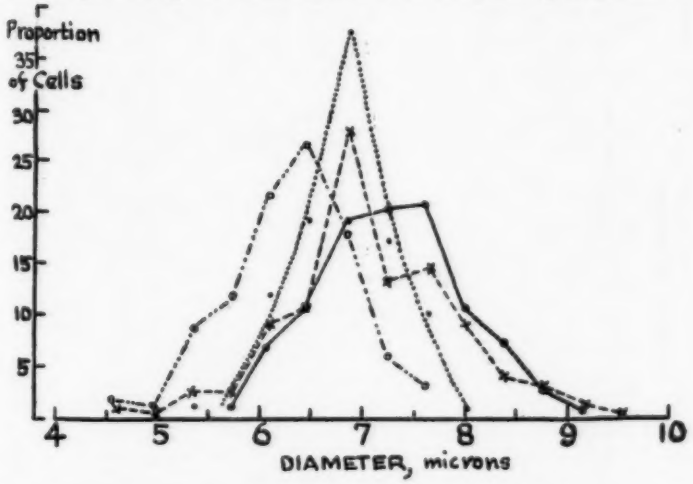

FIG. 3. DISTRIBUTION OF ERYTHROCYTE DIAMETERS IN THE BLOOD OF TWO TOTALLY GASTRECTOMIZED DOGS IN WHICH MACROCYTIC ANEMIA DEVELOPED FOLLOWING THE ADMINISTRATION OF CARBON TETRACHLORIDE, AND IN A TOTALLY GASTRECTOMIZED DOG IN WHICH SIMPLE MICROCYTIC ANEMIA DEVELOPED IN ASSOCIATION WITH SEVERE DISTEMPER

Dotted line: Blood of the normal dog—mean diameter (stained preparations) 6.81 μ. The actual determinations on which this smooth curve is based are represented by the black circles.

Continuous line: Blood of dog A 69 at the time when the erythrocyte count was 3.12 millions, mean corpuscular volume 77 c.μ and mean corpuscular diameter 7.29 μ.

Interrupted line: Blood of dog A 87 at the time when the erythrocyte count was 3.61 millions, mean corpuscular volume 74 c.μ and mean corpuscular diameter 7.07 μ.

Interrupted and dotted line: Blood of dog A 68 (distemper) at the time when the erythrocyte count was 3.54 millions, mean corpuscular volume 54 c.μ and mean corpuscular diameter 6.29 μ.

(1.3, 1.7, and 1.8 cc. per kgm., respectively), an amount which we have given repeatedly without the development of any symptoms whatever in normal dogs. The administration of carbon tetrachloride was followed by the refusal of all food, extreme lassitude, salivation, muscular twitching, and finally coma. One dog (A 67) died within 36

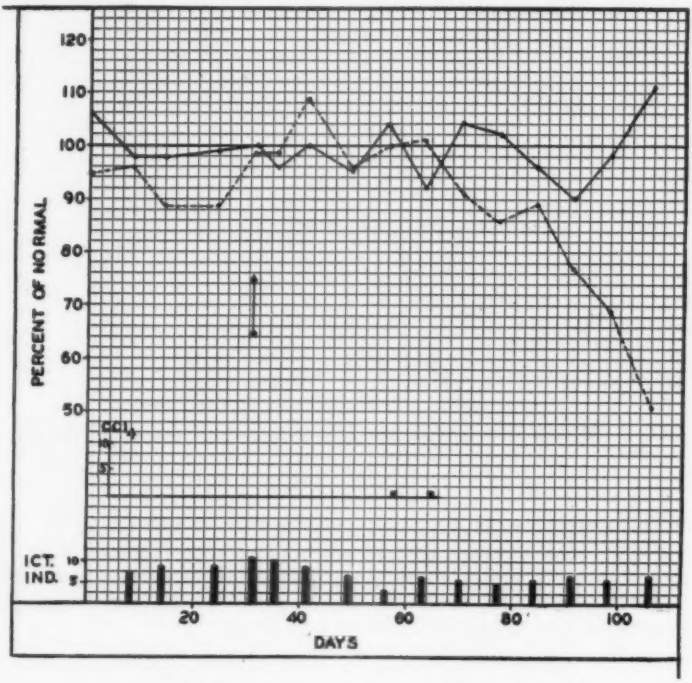

FIG. 4. CHANGES IN THE BLOOD OF DOG A 87

Arrow indicates day of operation.

Continuous line: mean corpuscular volume. *Interrupted line:* erythrocyte count.

All values are expressed in proportion to the normal.

hours, another (A 63) survived 7 days, while the third (A 69) was revived only by the administration of calcium gluconate intravenously. Dog A 63 developed jaundice on the third day following the giving of the drug and on the fifth day the icterus index was 100.

Dog A 69, which weighed 5.6 kgm., was subsequently given a total of 56 cc. of carbon tetrachloride in small doses over a period of 105 days. The changes in the blood of this dog are shown in figure 2. Fluctuations in the red cell count and hemoglobin occurred but these were, on the whole, of small magnitude until 26 days before death, when the erythrocyte count commenced to fall quite rapidly. At first no change was noted in the mean volume of the red corpuscles, but when the anemia became severe (R.B.C. 2.96) mean corpuscular volume increased to values of 80, 79, and 77 c.μ, which are distinctly higher than normal for the dog (47). The blood smears at this time showed an increase in anisocytosis with occasional distinct macrocytes and slight poikilocytosis. The mean diameter of the red blood cells was 7.29 μ as compared with 6.76 μ at the time of gastrectomy, and the Price-Jones curve showed a slight shift to the right (fig. 3). In spite of good appetite, this dog gradually lost weight (2.5 kgm.), became weaker and weaker, and finally died.

Dog A 87, weight 4.5 kgm., was given only two doses of carbon tetrachloride, the first dose of 1 cc. being given 26 days after operation and the second, of equal amount, one week later. These small amounts were followed by anorexia, and, because of our experience with the other dogs, no more of the drug was given. The changes which developed in the blood are shown in figure 4. Shortly after the administration of the last dose of carbon tetrachloride, the red cell count and hemoglobin decreased and, when the erythrocyte count had fallen to 2.61 million cells, the mean corpuscular volume was 74 c.μ. The blood at this time showed a moderate degree of anisocytosis with occasional macrocytes and slight poikilocytosis, and the mean diameter was 7.07 μ (fig. 3). Like A 69, this dog remained active to the end but became weaker and weaker. At death it weighed 3.7 kgm.

As judged by the color of the blood plasma and stools, the anemia which developed in both of these dogs was not hemolytic in nature. It was in these two dogs that the refractive index of the blood plasma was found to be lower than normal. The fall in refractive index preceded the development of anemia.

Only one partially gastrectomized dog (A 123) was given carbon tetrachloride. Treatment with this drug was commenced 86 days after operation. Doses of 2 to 5 cc. were given at weekly, biweekly, and finally triweekly intervals, and a total of 36 cc. was administered over a period of 7 weeks. Two days after the last dose the dog was found dead. No symptoms of illness had been noted, and no anemia had developed.

At *autopsy*, evidence of very severe liver damage was found in all of the animals treated with carbon tetrachloride. In the animal which had died within 36 hours following its administration (A 67), the necrosis was so widespread that practically no normal liver tissue remained (fig. 5, A^1 and A^2). The organ was yellowish in color and seemed smaller than normal. The liver architecture was completely

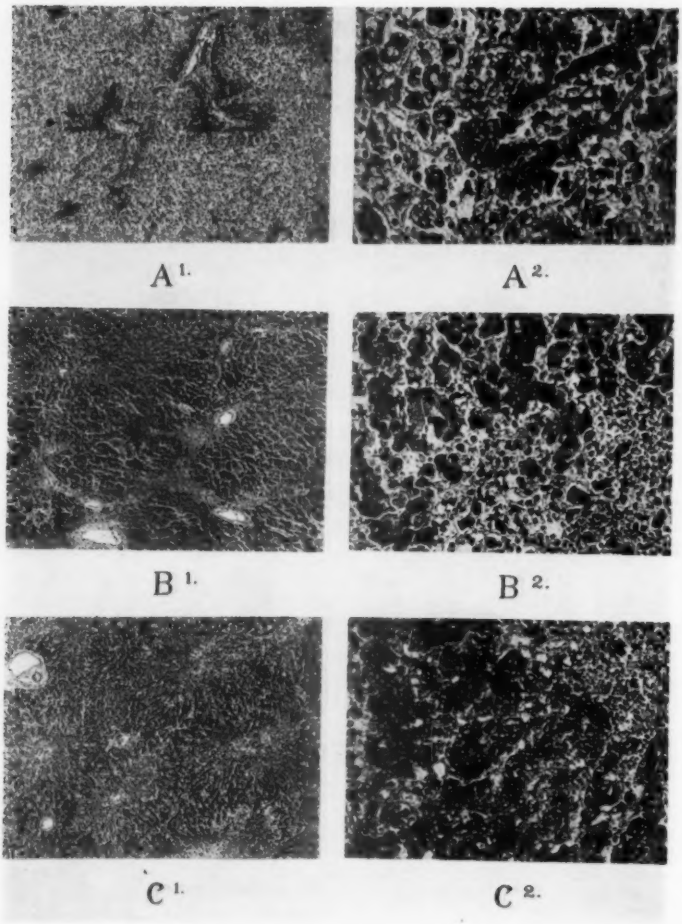

FIG. 5. PHOTOMICROGRAPHS OF SECTIONS OF THE LIVERS OF THREE TOTALLY GASTRECTOMIZED DOGS TREATED WITH CARBON TETRACHLORIDE

A^1 and A^2, low (×30) and high power (×195) views of the liver of A 67, which died 36 hours following the administration of 10 cc. Scarcely any normal liver cells remain.

B^1 and B^2, low and high power views of the liver of A 69, which received a total of 56 cc. over a period of 105 days.

C^1 and C^2, low and high power views of the liver of A 87, which received 2 cc. of carbon tetrachloride.

effaced. The nuclei of almost all of the liver cells had either entirely disappeared or were broken up or eccentric. The cytoplasm of the few liver cells which remained was granular or vacuolated. There had obviously been extensive collapse of liver tissue with extravasation of blood. A great deal of brown pigment was scattered throughout the sections.

The liver of the other dog which had died following the administration of 10 cc. of carbon tetrachloride (A 63) was deeply jaundiced. The microscopic appearance of the liver was similar to that of A 67, but the necrosis was less widespread and some scar tissue formation could be made out. The latter was interpreted as evidence of repair following liver necrosis associated with two attacks of distemper. The liver of dog A 68, which had died of distemper and had received no carbon tetrachloride, showed irregular foci of central necrosis and a moderate degree of fatty degeneration of the liver cells.

The liver of the dog (A 69) which developed macrocytic anemia after treatment with carbon tetrachloride for three months (figs. 2 and 3) weighed 110 grams, was pale in color and not nodular to touch. As in the dogs which had died immediately following the administration of carbon tetrachloride, there was widespread destruction of liver tissue with collapse and disorganization of the normal liver architecture (fig. 5, B^1 and B^2). The capillaries and sinuses were dilated with blood and there was extensive deposition of brown pigment, chiefly within the mononuclear phagocytes. A great proportion of the liver cells were destroyed and in many of those which remained the nuclei were eccentric and the cytoplasm was very granular. There was only a slight degree of fresh connective tissue proliferation.

The liver of the dog which developed macrocytic anemia after receiving only a small amount of carbon tetrachloride (A 87, figs. 3 and 4) weighed 156 grams, was pale and only moderately firm. On microscopic examination (fig. 5, C^1 and C^2) even more extensive necrosis of liver tissue was found than in the liver of A 69. The liver structure was collapsed, the sinuses and capillaries were dilated or ruptured. Erythrocytes could even be seen between columns of liver cells. The hepatic cells which remained showed a marked degree of vacuolization and granulation of the cytoplasm and their nuclei were eccentric, pyknotic, or fragmented.

The liver of the partially gastrectomized dog (A 123) was pale, brownish in color, and slightly resistant on cutting. The microscopic picture was similar to that of dogs A 69 and A 87.

Examination of sections of these livers stained with van Gieson's solution revealed practically no connective tissue formation except in the liver of dog A 87 where a small amount was present in some of the portal areas.

The spleens of these animals showed varying degrees of hemosiderosis. In dog A 87 this was extreme, but in dog A 69 it was relatively slight in amount.

Bone marrow was taken from a femur and a rib of each dog. In all instances the rib marrow was red in color. That of the femur was largely composed of fat. Microscopically, small islands of nucleated red corpuscles and leukocytes were

found in the femoral marrow, whereas the rib marrow was composed chiefly of blood cells and showed little fat. From a comparison of the nucleated red corpuscles present in the bone marrows of dogs A 68 and A 69, which developed microcytic and macrocytic anemia, respectively, one gained the impression that macroblasts were somewhat more numerous in the marrow of the latter than in that of the former, but the difference was not striking. Satisfactory sections for the microscopic study of the bone marrow of dog A 87 were not obtained.

Except as already stated, there were no other noteworthy findings at autopsy. No evidence of bleeding into the gastro-intestinal tract, no stricture or dilatation of the duodenum, nor sign of intra-abdominal infection was discovered. The lungs of dog A 68 showed consolidation on both sides.

THE CAUSE OF SENSITIVENESS TO CARBON TETRACHLORIDE IN GASTRECTOMIZED DOGS

In order to determine whether gastric juice in some way influences the toxicity of carbon tetrachloride, two normal dogs were given 8 cc. of the drug per kgm. body weight; that is, 108 and 110 cc. respectively. In one instance, however, the drug was first mixed with 75 cc. of normal canine gastric juice, obtained by histamine stimulation and free of food particles. This was allowed to stand thirty minutes and was then given by stomach tube. No untoward symptoms other than listlessness followed the administration of these huge doses. For two days the dogs refused food. At the end of five days they were sacrificed. By this time they had regained their appetites but were still somewhat inactive.

The livers of both dogs were dark red in color. In both there was extensive necrosis of the liver cells in the centres of the liver lobules, and the cells which remained showed cloudy swelling and some vacuolization. The cloudy swelling and fatty degeneration seemed to be somewhat more marked in the liver of the dog which had received no gastric juice, but the total amount of remaining liver tissue seemed to be equal to or greater than that of the other dog. This experiment therefore failed to show that gastric juice decreases the toxicity of carbon tetrachloride.

Robbins (37) has demonstrated that little, if any, carbon tetrachloride is absorbed from the stomach and that most of it is absorbed from the small intestine. It seemed probable, therefore, that absorption is more rapid in the gastrectomized dog. To test this hypothesis, carbon tetrachloride, 1.6 cc. per kgm. body weight, was injected by hypodermic needle into the first portion of the duodenum of three dogs and into the stomach of two animals. In each animal an abdominal incision was made under ether anesthesia and the drug injected directly. This method was chosen because it was found that duodenal intubation could not be carried out with certainty. The treatment of each dog during the whole experiment was exactly the same. As an additional control, two dogs were each given 1.6 cc. carbon tetrachloride per kgm. of body weight by stomach tube and were not operated upon.

All seven dogs were sacrificed at the end of 48 hours. The livers of the animals which had received carbon tetrachloride by injection directly into the stomach or duodenum were rather soft and, on cutting, blood oozed freely. The livers of the dogs which had received carbon tetrachloride by stomach tube were perhaps firmer, but their gross appearance was not strikingly different from that of the livers of the other dogs.

On *microscopic examination*, central necrosis was present in the liver lobules in all the sections. This varied in extent, but there appeared to be distinctly more destruction of liver cells in the livers of the dogs which had received intra-duodenal injections than in the livers of the other dogs. An estimate of the degree of damage, made without knowledge of the form of treatment each animal had received, revealed an average of 40 per cent destruction in the livers of the dogs which had received carbon tetrachloride by stomach tube, 50 per cent in the livers of the animals which had been given the drug by direct injection into the stomach, and 80 per cent in the group which had received intra-duodenal injections.

It is well known (50) that the diet is of great importance in determining the toxicity of carbon tetrachloride. In order to ascertain what influence the diet the gastrectomized dogs received may have had in causing their susceptibility to the toxic effects of the drug, two normal animals were fed, for 33 and 47 days, respectively, milk and oxtail soup in the quantities taken by the gastrectomized dogs. In addition, in order to imitate as far as possible the conditions to which the gastrectomized dogs had been subjected, before the special diet was instituted each dog was anesthetized for two hours, 50 cc. of blood were withdrawn, and no food whatever was given for two days. At the end of the stated periods of time, 1.6 cc. carbon tetrachloride per kgm. body weight was given each dog by stomach tube.

In striking contrast to the effects of this dose in the totally gastrectomized animals, no untoward symptoms whatever were observed. The animals continued to eat normally and did not even show any listlessness. Their blood plasma, examined two and seven days following administration of the drug, showed no bilirubinemia. At the end of seven days the dogs were killed. Gross examination of their livers revealed no noteworthy changes. The degree of liver cell necrosis observed on microscopic examination was about the same as had followed the administration by stomach tube of the same dose of carbon tetrachloride to control dogs on a normal diet.

These experiments suggest, therefore, that rapid absorption of carbon tetrachloride from the duodenum is probably the major cause of the extreme sensitivity of totally gastrectomized dogs to this drug.

DISCUSSION

The high operative mortality associated with total gastrectomy in the dog and the extreme sensitivity of gastrectomized dogs to orally

administered carbon tetrachloride, which we discovered accidentally, have limited our observations considerably. They tend to show, nevertheless, that slight normocytic anemia develops spontaneously in dogs following total gastrectomy. So little blood was lost at operation that this was not, we believe, a factor in the production of the anemia. There was no postoperative bleeding from the line of anastomosis, as evidenced by the character of the stools. Furthermore, three dogs subjected to subtotal gastric resection and an equal degree of blood loss, did not develop anemia, although they were observed as long as, or longer than, the dogs whose stomachs were totally excised.

The development of moderate, and severe anemia in two totally gastrectomized dogs during attacks of distemper tends to confirm Ivy's opinion (20) that "the excision of the stomach just about annuls the factor of safety in digestion," and that any burden in excess of the average is likely to lead to the appearance of anemia. We have observed distemper in normal dogs, and very slight or no anemia has developed. Evidence of a similar character is that of Mullenix *et al.* (34), who found that the gastrectomized dog has a greatly reduced capacity for regenerating hemoglobin after blood loss.

In view of the readiness with which the totally gastrectomized dog develops anemia, it is not surprising that anemia occurred in the two dogs which survived drug-induced liver damage. It is of interest, however, that this anemia was macrocytic in its terminal stages rather than microcytic as in the dog with severe anemia following distemper. The cause of this difference is questionable. It does not, of course, necessarily follow that the anemia was the result of a severe deficiency of antianemic principle. Unfortunately, the dogs died before it was possible to test the efficacy of liver extract in relieving the anemia. It is possible that the anemia was the direct result of injury to the bone marrow by the carbon tetrachloride. However, there was no evidence of aplasia of the bone marrow. It may be further pointed out that in dogs which had not been operated upon such anemia has not developed following the administration of the relatively small quantities of carbon tetrachloride given to the totally gastrectomized dogs (40). Only following the administration of much greater doses over longer periods of time, and with the production of widespread

liver damage, has macrocytic anemia developed (40). It seems probable to us, therefore, that the macrocytic anemia occurred as the result of the combined effects of total gastrectomy and extensive liver damage.[3]

SUMMARY

1. Total gastrectomy was performed in 19 dogs and, in 3 more, partial gastric resection was carried out.

2. In 6 of 7 dogs which survived total gastrectomy, slight normocytic anemia developed.

3. The development of distemper in two of these dogs was associated with aggravation of the anemia, which became microcytic in character. This is contrasted with the failure to develop anemia in association with distemper in dogs which have not been operated upon.

4. The totally gastrectomized dogs were extremely sensitive to carbon tetrachloride administered orally. This is believed to be due at least in part to rapid absorption of the drug from the duodenum.

5. In two totally gastrectomized dogs treated with small doses of carbon tetrachloride, severe anemia, macrocytic in its later stages, developed. Extensive liver damage was found at autopsy.

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[3] In a preliminary report (*Proc. Staff Meet. Mayo Clinic*, **10**: 429 (July 3) 1935) Higgins and Stasney have recently described macrocytic anemia in rats following the production of typical atrophic cirrhosis of the liver by inhalation of fumes of carbon tetrachloride.

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BOOK REVIEW

Textbook of Biochemistry. By BENJAMIN HARROW and CARL P. SHERWIN. 1935. 797 pp. $6.00. (*W. B. Saunders Co., Phila., Pa.*)

"Biochemistry, like several other branches of science, has become so encyclopedic in its scope, that it seems an impossible task for any one individual to write an adequate textbook." This statement by the editors in the preface explains why this book was written by thirty specialists in the various fields of biochemistry. One wonders after reading this work whether it may not also be an impossible task for thirty individuals to write an adequate textbook. There is a lack of unity and perspective for the subject as a whole which is an essential part of a good textbook. Unnecessary duplication of treatment of the same subject appears throughout the book, the different authors apparently being unaware of the others' contributions to that subject. On the other hand, one searches hard for an adequate treatment of other subjects, finding only a little here and a little there. Some of the chapters are excellently written; others are poorly executed. Undue emphasis with regard to the field as a whole upon certain subjects in which the author is a specialist may prove misleading to the student.

Though less desirable as a textbook, medical students will find this work of value for reference purposes.

E. G. B.

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THE FIRST QUARTER-CENTURY OF THE JOHNS HOPKINS HOSPITAL

1889-1914

By Henry Mills Hurd, M.D., *First Superintendent of The Johns Hopkins Hospital.* Edited and extended by Lewellys F. Barker, M.D. To be illustrated.

CONTENTS: I. The Certificate of Incorporation of The Johns Hopkins Hospital. II. The Original Board of Trustees of the Hospital. III. The Site of the Hospital. IV. The Planning of the Hospital. V. The Adviser of the Board of Trustees, Dr. John Shaw Billings. VI. The Building of the Hospital. VII. The Organization of the Hospital and Its Administration. VIII. The First Director of the Hospital, Dr. Daniel Coit Gilman. IX. The First Superintendent of the Hospital, Dr. Henry Mills Hurd. X. The Staff of "Consulting Physicians." XI. The Extensions of the Hospital Made Between 1889 and 1914. XII. Diary (1899–1914). XIII. The Department of Pathology. XIV. The Department of Medicine. XV. The Department of Surgery. XVI. The Department of Gynecology. XVII. The Four Doctors: Dr. William Henry Welch, Dr. William Osler, Dr. William Stewart Halsted, Dr. Howard Atwood Kelly. XVIII. The Out-Patient Service (Dispensary). XIX. The Department of Obstetrics. XX. The Department of Pediatrics and the Harriet Lane Home for Invalid Children. XXI. The Department of Psychiatry and the Henry Phipps Psychiatric Clinic. XXII. The Phipps Tuberculosis Dispensary. XXIII. The Training School for Nurses. XXIV. The Library of the Hospital. XXV. The Department of Social Service. XXVI. The Department of Art in Medicine. XXVII. The Publications of the Hospital. XXVIII. The Trustees and Officers of the Hospital (1889–1914). XXIX. Deceased Members of the Board of Trustees. XXX. Donations to the Hospital (1889–1914).

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